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Uterine Artery Doppler in Women with History of Previous Pre-eclampsia and Women with Chronic Hypertension: Re-evaluation of a Prognostic Value in a High-Risk Population

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Abstract

Objective: To evaluate the prognostic role of uterine artery Doppler for pre-eclampsia in high-risk patients. Because of the higher prevalence of new onset of disease in a high-risk population, a better performance could be expected in this special group.

Methods: This retrospective study compares uterine artery Doppler to predict pre-eclampsia in patients with a history of pre-eclampsia and also in patients with chronic hypertension, both with high-risk to develop recurrent, superimposed or new onset pre-eclampsia. Doppler measurements of uterine arteries were performed every 4 weeks in the 1st and 2nd trimester.

Results: Pre-eclampsia occured in 33% of current high-risk pregnancies. The best performance for the prediction of pre-eclampsia was provided by bilateral notching plus increased PI ≥ 2.5, both in the 1st and 2nd trimester. In the 1st trimester the specifity was 81% (95% CI: 58-95) in the Prior PE group and 95% (95% CI: 74-100) in the C. H. group. In the 2nd trimester the sensitivity was 97% (95% CI: 86-100) in the Prior PE group and 100% (95% CI: 93-100) in the C. H. group. Sensitivity was very low in the 1st and 2nd trimester.

Conclusion: Our results show, that the negative predictive value of uterine artery Doppler works well even in a high-risk group. Data however suggest relative poor positive predictive value of uterine artery Doppler even in a high-risk population using a cut-off of 2.5 PI. A value of the uterine artery Doppler using a high cut-off might be in the increased specifity. Nevertheless, a combination of the uterine artery Doppler with biochemical markers and maternal parameters seems to be essential.

Keywords: Pre-eclampsia; High-risk pregnancies; Uterine artery Doppler

Introduction

Pre-eclampsia occurs in about 5-8% of pregnancies and causes at least 50.000 maternal deaths every year throughout the world [1-4]. Inadequate trophoblast invasion leads to placental hypoperfusion and diffuse maternal endothelial cell damage and underlies the clinical characteristics of pre-eclampsia and Intrauterine growth restriction (IUGR) [5-8]. Several studies reported on biochemical and biophysical markers which could potentially identify pregancies in the 1st trimester that subsequently develop pre-eclampsia [9-27]. Early risk estimation would allow more individualized prenatal care by reduction of routine visits for the majority of women classified as being at low risk for pregnancy complications. At the same time surveillance in specialist clinics would be more readily available for women at high risk; for example women with a history of previous pre-eclampsia. Furthermore, low-dose acetylsalicylic acid treatment could be initiated early in pregnancy and potentially half the risk for subsequent development of pre-eclampsia [10,14,17,28-31]. Uterine artery (UtA) Doppler velocimetry reflects the utero-placental blood flow and seems to be a good, non-invasive prognostic tool in the prediction of adverse pregnancy outcomes, especially pre-eclampsia and IUGR. In industrialized countries UtA Doppler can be easily performed at routine visits without significant loss of time and without significant extra costs, respectively. In normal pregnancies trophoblast invasion leads to vascular remodelling; the maternal spiral arteries undergo conversion from low-capacity, high-resistance vessels to high-capacity, low-resistance vessels (14-20 weeks of gestation) [5,27]. This process is reflected in decreasing impedance to flow and increasing diastolic flow velocity on Doppler examination of the uterine arteries. If this process is restricted because of impaired trophoblast invasion, the uteroplacental circulation remains in a state of high-resistance and low flow. In Doppler this is reflected by persisting increased impedance to flow and persistent notching. Rarely notching can be present until 26 weeks of gestation without pathological cause. In general, increased indices and the presence of end-diastolic notching >17 weeks of gestation reflect increased impedance in materno-placental circulation and signify increased risk for pre-eclampsia [32-36]. However studies in a low-risk population showed a poor predictive value [11,29,37-39]. It is well known that in the first trimester and early second trimester (<17 weeks) there is a considerable overlap between normal and pregnancies that go on later to develop pre-eclampsia both in the presence of notching and in PI values. The performance of UtA Doppler alone as screening marker increases gradually in the second trimester.

The aim of this study was to assess the prognostic role of UtA Doppler in a high risk population to predict pre-eclampsia by selecting a high PI value for cut-off to increase specifity. Predictive values depend on the prevalence [40], because a better performance in this special group could be expected.

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Patients and Methods

The study examined pregnancies with high risk to develop pre-eclampsia (WHO 2011), followed in a special care center of the Department of Obstetrics and Gynecology at the Medical University of Graz. UtA Doppler was measured every 4 weeks in two groups of patients: one group with a history of pre-eclampsia (=group Prior PE) and a second group of patients with chronic hypertension (=group C. H.). From a systematic search within the patient records (electronic documentations systems Viewpoint Fetal Database, GE Healthcare and open Medocs (Hospital Management and Patient Medical Documentation System) and the written visit protocols of the outpatient department for hypertension) between the years 2006 and 2012, 1207 pregnancies were identified. The selection criteria were the following: if UtA Doppler was carried out in 1st and/or 2nd trimester; patients met criteria for one or both study groups. Patients who did not deliver at our department were excluded because of missing outcome data. A total of n=139 patients was included in the study and separated into two groups: 1) Prior PE (n=61) contained patients with a history of previous pre-eclampsia and 2) C. H. (n=78) consisted of pregnancies with chronic hypertension. Pregnant women with multiple risk factors were not excluded but other risk factors like pregestational diabetes, obesity, thrombophilia, renal or autoimmune disease [41] were not evaluated. Patients who met the criteria for both groups, got assigned to group Prior PE because of a higher relative risk to develop pre-eclampsia.

Since 2006 all of our patients with a history of pre-eclampsia receive a prophylaxis with low-dose aspirin. This means that all patients in the Prior PE group received low-dose aspirin prophylaxis and none of the patients in group C. H. received prophylaxis. An eventually given prophylaxis was not considered in the assessment of the test performance.

Measurements

Doppler examinations of both uterine arteries were performed by experienced sonographers, certificated by the Fetal Medicine Foundation (FMF) London. Pulsed wave Doppler (Voluson E8, GE Healthcare and Siemens Antares) were used with the sampling gate set at 2 mm. At the smallest possible angle of insonation (at least<50 deg) color flow mapping was used to identify the left and right uterine arteries [42]. Since 2012 a new site of measurement for the UtA Doppler measurements in the 1st trimester has been recommended, i. e. the ascending branch of the uterine artery at the level of the internal cervical os. The study of Lefebvre et al. showed that in the 1st trimester Doppler measurements at the crossover of the uterine artery with the external iliac artery result in significant lower PI-values than measurements at the level of the internal cervical os [43]. Our measurements were performed at the level of the apparent crossover with the external iliac artery, because the new recommendations had not been yet published prior to the study period. Pulsatility index (PI) was measured and the presence of diastolic notching was recorded when three consecutive waveforms free of artifacts were obtained. Only bilateral notching and increased PI were rated as pathological. Similar to most recent studies increased PI was defined as a PI max. >95th percentile as recommended by PIA-Viewpoint reference charts. A potential standardized cut-off value is currently being discussed.

Outcome

Pregnancy outcome was analysed for pre-eclampsia. Diagnostic criteria [2]: Mild pre-eclampsia: BP>140-160/90-110 mmHg, proteinuria 0.3-5 g/24 h; Severe pre-eclampsia: BP>160/110 mmHg, proteinuria>5 g/24 h or oliguria<0.4 l/24 h, thrombocytopenia, elevated liver enzymes, elevated serum creatinine, neurological symptoms, epigastric or right upper quadrant pain, or IUGR (<10th percentile); Eclampsia: additional occurence of seizures not attributable to other causes; HELLP-Syndrome: elevated liver enzymes, thrombocytopenia<100.000/µl; Superimposed pre-eclampsia: chronic hypertension, BP>140/90 mmHg, proteinuria>0.3 g/24 h.

Statistics

The statistical software package SPSS 20 (SPSS Inc. Chicago, II.) was used for data analyses: contingency tables, rates, confidence intervals, descriptive statistics (mean,median). Sensitivity, specifity, PPV (=positive predictive value) and NPV (=negative predictive value) were calculated to evaluate the prognostic role of uterine artery Doppler.

Results

34% (47/139) of identified participants developed pre-eclampsia. In the Prior PE group 24 women out of 61 (39%) developed pre-eclampsia (17% mild pre-eclampsia, 8% severe pre-eclampsia, 8% HELLP-Syndrome, 67% superimposed pre-eclampsia). In the C. H. group 23 women out of 78 (29%) developed pre-eclampsia (9% HELLP-Syndrome, 91% superimposed pre-eclampsia). First trimester UtA Doppler was carried out in 28 out of 61 (46%) within the Prior PE group and in 22 patients out of 78 (28%) within the C. H. group. Second trimester UtA Doppler was carried out in 61 patients out of 61 within the Prior PE group (100%) and in 73 patients out of 78 (94%) within the C. H. group.

First trimester

In the Prior PE group bilateral notching was present in 18 women out of 28 (64%). 28% of these (5/18) subsequently developed pre-eclampsia. Patients without the presence of notching (36%, 10/28) developed pre-eclampsia in 10% of cases (1/10). In the C. H. group notching was present in 7 women out of 22 (32%), it was not present in 15 women out of 22 (68%). 14% of patients (1/7) with notching and 13% of patients (2/15) without notching subsequently developed pre-eclampsia (Figure 1).

Within the Prior PE group mean PI was 1.7 in the right uterine artery (SD ± 0.7) and 1.7 in the left uterine artery (SD ± 0.9). In the C. H. Group the corresponding values were 1.3 in the right uterine artery (SD ± 0.5) and 1.2 in the left uterine artery (SD ± 0.4). Maximum and minimum PI values in the Prior PE group were 3.4 and 0.43 in the right uterine artery and 4.9 and 0.47 in the left uterine artery. In the C. H. group maximum and minimum values were 2.1 and 0.5 in the right

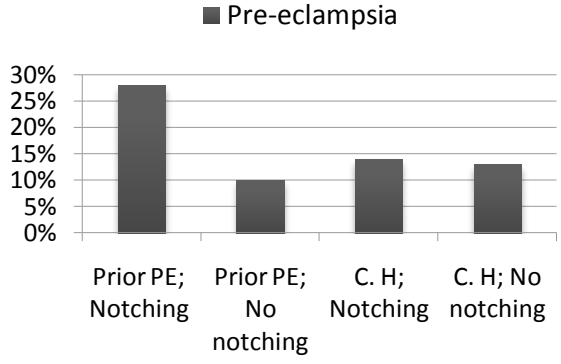

Figure 1: First-trimester bilateral notching and subsequent development of pre-eclampsia.

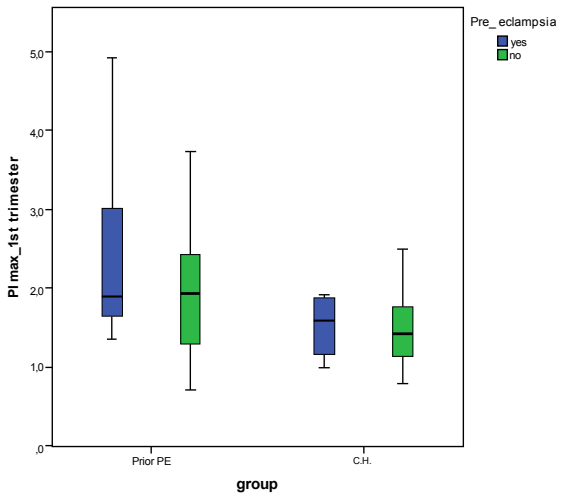

Figure 2: First trimester PI max. in relation to pre-eclampsia.

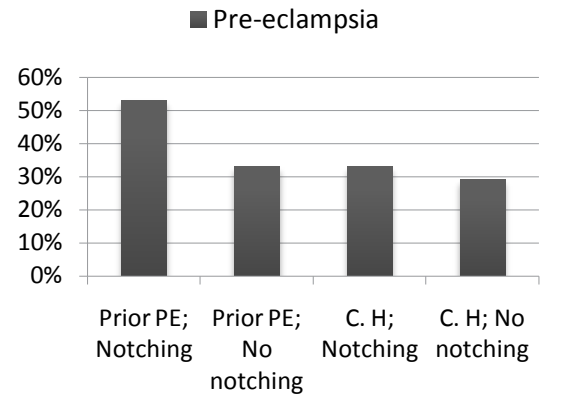

Figure 3: Second-trimester bilateral notching and subsequent development of pre-eclampsia.

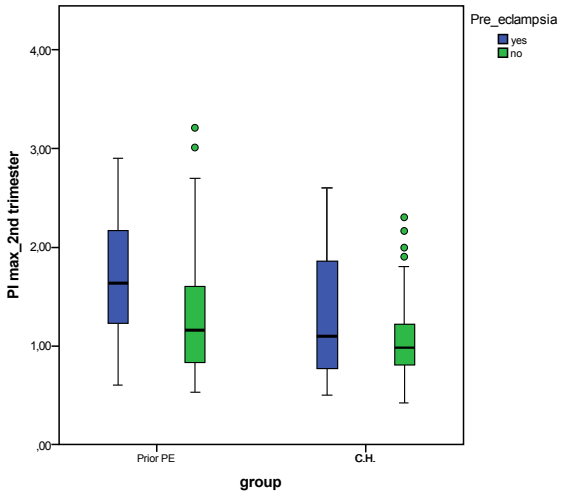

Figure 4: Second trimester PI max. in relation to pre-eclampsia.

uterine artery, 2.5 and 0.4 in the left uterine artery. PI max. values in relation to subsequently developed pre-eclampsia are shown in Figure 2.

Second trimester

In the Prior PE group notching was present in 19/61 cases (31%), the remaining 42 patients (69%) had no bilateral notching. Patients with notching subsequently developed pre-eclampsia in 10/19 cases (53%). Patients without notching developed pre-eclampsia in 14/42 cases (33%). In the C. H. group notching was present in 18/73 cases (23%), in 55/73 cases (71%) notching was absent. Pre-eclampsia subsequently developed 6 women out of 18 women with notching (33%) and 16 women out of 55 women (29%) without notching (Figure 3).

Mean PI in the Prior PE group was 1.2 in the right uterine artery and 1.2 in the left uterine artery (SD ± 0.6, respectively). The mean PI in the C. H. group was 1.0 in each uterine artery (SD ± 0.5). In the Prior PE group maximum and minimum PI values were 3.0 and 0.33 in the right uterine artery, 3.2 and 0.4 in the left uterine artery. In the C. H. group maximum and minimum values were 2.3 and 0.4 in the right uterine artery, 2.6 and 0.4 in the left uterine artery. Relation between PI max.values and pre-eclampsia is shown in Figure 4.

Prognostic role

Predictive values were calculated for bilateral notching (irrespective increased PI values); increased maximum PI ≥ 2.5 (irrespective notching); increased maximum PI ≥ 2.5 and bilateral notching; bilateral notching and/or PI ≥ 2.5. The best performance was provided by bilateral notching. A PI ≥ 2.5 was used to increase specificity at a trade-off for sensitivity in an attempt to better separate pre-eclampsia predictiction from normal pregnancies.

First trimester

In the Prior PE group bilateral notching reached a sensitivity of 83% (95% confidence interval (95%CI): 36-100%), a specifity of 43% (95%CI: 22-66%), a PPV of 29% (95%CI: 10 56%) and a NPV of 90% (95%CI: 55-100%). In the C. H. group sensitivity was 40% (95%CI: 05-85%), specifity 67% (95%CI: 41-87%), PPV 25% (95%CI: 03-65%) and NPV 80% (95%CI: 52-96%).

Second trimester

In the Prior PE group bilateral notching achieved a sensitivity of 40% (95%CI: 21-61%), a specifity of 78% (95%CI: 61-90%), a PPV of 56% (95%CI: 31-78%) and a NPV of 65%(95%CI: 49-79%). In the C.H. group bilateral notching reached a sensitivity of 35% (95%CI: 16-57%), a specifity of 71% (95%CI: 57-82%), a PPV of 33% (95%CI: 16-55%) and a NPV of 72% (95%CI: 58-84%). More predicitve values are summarized in Table 1. The predictive values for IUGR were also calculated, but are not presented due to the very small number of IUGR cases (13 fetuses). Regarding the calculation which has taken into acount PI values, note the comment in the discussion (Table 2).

Discussion

The poor predictive value of UtA Doppler velocimetry in a low-risk population is generally known. Therefore, a routine screening using uterine artery Doppler in the general population is not recommended. There are just a few studies that evaluated the predictive value of UtA Doppler alone in a high-risk population. Different concepts and definitions of abnormal results, the heterogenity of methodologies especially for first trimester UtA Doppler, missing details, and unknown inclusion and exclusion criteria, make the comparison of data difficult.

Predictive values for bilateral notching were calculated in this study; for increased max. PI ≥ 2.5, max. PI ≥ 2.5 and bilateral notching and for bilateral notching and/or max. PI ≥ 2.5. We had to be careful

		Sensitivity % (95 % CI)	Specifity % (95 % CI)	PPV % (95 % CI)	NPV % (95 % CI)	Prevalence % (95 % CI)
Notching, 1st trimester	Pre-eclampsia	67[1] (30-93)	54 (37-69)	24 (09-45)	88 (69-97)	18 (09-31)
		83[2] (36-100)	43 (22-66)	29 (10-56)	90 (55-100)	22 (09-42)
		40[3] (05-85)	67 (41-87)	25 (03-65)	80 (52-96)	22 (07-44)
Notching, 2nd trimester	Pre-eclampsia	35 (21-50)	76 (66-85)	43 (27-61)	69 (59-78)	34 (26-43)
		40 (21-61)	78 (61-90)	56 (31-78)	65 (49-79)	41 (29-54)
		35 (16-57)	71 (57-82)	33 (16-55)	72 (58-84)	29 (20-41)
PI ≥ 2.5, 1st trimester	Pre-eclampsia	22 (03-60)	88 (73-96)	29 (04-71)	83 (69-93)	18 (09-32)
		33 (04-78)	81 (58-95)	33 (04-78)	81 (58-95)	22 (09-42)
		00 (00-71)	95 (74-100)	00 (00-97)	86 (64-97)	14 (03-35)
PI ≥ 2.5, 2nd trimester	Pre-eclampsia	07 (01-18)	98 (92-100)	60 (15-95)	67 (58-75)	34 (26-43)
		08 (01-27)	95 (82-99)	50 (07-93)	61 (48-74)	39 (27-53)
		05 (00-23)	100 (93-100)	100 (03-100)	71 (59-81)	30 (20-42)
PI ≥ 2.5 + Notching, 1st trimester	Pre-eclampsia	22 (03-60)	88 (73-96)	29 (04-71)	83 (69-93)	18 (09-32)
		33 (04-78)	81 (58-95)	33 (04-78)	81 (58-95)	22 (09-42)
		00 (00-71)	95 (74-100)	00 (00-97)	86 (64-97)	14 (03-35)
PI ≥ 2.5 + Notching, 2nd trimester	Pre-eclampsia	04 (01-15)	99 (94-100)	67 (09-99)	66 (58-74)	34 (26-43)
		04 (00-21)	97 (86-100)	50 (01-99)	61 (47-73)	39 (27-53)
		05 (00-23)	100 (93-100)	100 (03-100)	71 (59-81)	30 (20-42)
Notching and/or PI ≥ 2.5, 1st trimester	Pre-eclampsia	67 (30-93)	53 (36-86)	24 (09-45)	88 (68-97)	18 (09-32)
		83 (36-100)	43 (22-66)	29 (10-56)	90 (55-100)	22 (09-42)
		33 (01-91)	63 (38-84)	13 (00-53)	86 (57-98)	14 (03-35)
Notching and/or PI ≥ 2.5, 2nd trimester	Pre-eclampsia	37 (23-52)	75 (65-84)	44 (28-60)	69 (59-79)	34 (26-43)
		46 (26-76)	73 (56-86)	52 (30-74)	68 (51-81)	39 (27-53)
		27 (11-50)	76 (63-87)	33 (13-59)	71 (57-82)	30 (20-42)

[1]Total population
[2]Group Prior PE
[3]Group C. H.

Table 1: Summary of predictive values.

		True positive	False negative	False positive	True negative
Notching, 1st trimester	Pre-eclampsia	6[4]	3	19	22
		5[5]	1	12	9
		2[6]	3	6	12
Notching, 2nd trimester	Pre-eclampsia	16	30	21	67
		10	15	8	28
		8	15	16	39
PI ≥ 2.5, 1st trimester	Pre-eclampsia	2	7	5	35
		2	4	4	17
		0	3	1	18
PI ≥ 2.5, 2nd trimester	Pre-eclampsia	3	43	2	86
		2	22	2	35
		1	21	0	51
PI ≥ 2.5 + Notching, 1st trimester	Pre-eclampsia	2	7	5	35
		2	4	4	17
		0	3	1	18
PI ≥ 2.5 + Notching, 2nd trimester	Pre-eclampsia	2	44	1	87
		1	23	1	36
		1	21	0	51
Notching and/or PI ≥ 2.5, 1st trimester	Pre-eclampsia	6	3	19	21
		5	1	12	9
		1	2	7	12
Notching and/or PI ≥ 2.5, 2nd trimester	Pre-eclampsia	17	29	22	66
		11	13	10	27
		6	16	12	39

[4]Total population
[5]Group Prior PE
[6]Group C. H.

Table 2: True positives, false negatives, false positives, true negatives.

in interpretation of cases when PI was taken into account. The documented PI values are difficult to interpret because permanent change of cut-off values and measurement sites in the literature in the last few years lead to some confusion in assessment and documentation. Permanently changing knowledge is reflected in inconsistent data basis throughout the literature. This is one of the reasons why the predictive

values of PI are only a rough estimate. This fact might also explain why our results don´t match the results of similar recent studies. Therefore a detailed interpretation of our PI measurements is provided. The best performance in our study was provided by bilateral notching and bilateral notching and/or max. PI ≥ 2.5. These two parameters could be considered equal. The comparison of the prognostic potential of increased PI and bilateral notching was not consistent partly because of the mentioned issues.

This study has several limitations, like the documentation of PI values. We could not find differences between early-onset and late-onset pre-eclampsia due to the low number of patients. Furthermore, an eventually given prophylaxis was not considered.

First trimester

The sensitivity of the UtA Doppler was higher in the first trimester than in the second trimester. This finding is consistent with previous studies concluding that early notching alone is unlikely to be useful in the prediction of pre-eclampsia and other avderse pregnancy outcomes due to the high prevalence of notching in normal pregnancies [44]. Vainio et al. did a prospective study with 120 pregnant women at high-risk to develop pre-eclampsia. They reported a sensitivity of 91% and a speciftiy of 46% for bilateral notching [45]; Herraiz et al. found the sensitivity for the prediction of early pre-eclampsia at 90% and the speciftiy at 33%. They included pregnant women with chronic hypertension, a history of pre-eclampsia or IUGR, diabetes, chronic renal disease, BMI<30 kg/m^2, inherited or acquired thrombophilia and autoimmune disease [46]; Cnossen et al. reported a sensitivity of 91% with a specifity of 46% for first-trimester bilateral notching [37]; Prefumo et al. reached a sensitivity of 75% and a NPV of 88%. This study included only patients with a history of previos pre-eclampsia and evaluated the predictive value for adverse pregnancy outcome <37 weeks of gestation. Adverse pregnancy outcomes were pre-eclampsia, IUGR, placental abruption and intrauterine fetal death [47]; Most studies reported a high sensitivity and a low specifity for bilateral notching. Gomez et al. reported a sensitivity of 24% and a specifity of 95,1% for a PI >95th percentile. At 11-14 weeks of gestation their 95th percentiles for UtA mean PI were between 2.38 and 3.13, similar to our PI cut-off value which was 2.5. Their results are also similar to ours. We reached a sensitivity of 33% and a specifity of 81% in the Prior PE group [48] (Table 1).

Second trimester

In our study second trimester UtA Doppler reached a very high specifity, but a low sensitivity, similar to other previous studies. In our study the specifity was 97% (95% CI: 86-100) in the Prior PE group and 100% (95% CI: 93-100) in the C. H. group. Vainio et al. reported a sensitivity of 36% and a specifity of 82% [45]; Axt-Fliedner et al. tested various UtA Doppler ultrasound markers in a prospective study with 52 pregnant women who had one of the following risk factors: chronic hypertension, history of pre-eclampsia, IUGR, intrauterine death or placental abruption. Bilateral notching reached a sensitivity of 25% and a specifity of 71% [49]; Cameroni et al. reported a sensitivity of 57%, a specifity of 82% and a PPV of 61%. Risk population was composed of women with chronic hypertension, history of previous pre-eclampsia, stillbirth, placental abruption and small for gestational age neonates. In contrast to our study, they reached better predictive values which could be explained by their definition of abnormal UtA Doppler. UtA Doppler was rated pathological when RI (resistance index) was >0.58 and/or when bilateral notching was recorded. Furthermore, they did not differentiate between pre-eclampsia and IUGR. So the test was correct positive when pre-eclampsia was diagnosed with or without IUGR, but also when IUGR was diagnosed without pre-eclampsia [50]. We evaluated the prognostic role of UtA Doppler separated for prediction of pre-eclampsia first and then for prediction of IUGR; Asnafi et al. did a prospective study with 70 high-risk pregnancies. They reported a specifity of 73% and a relative high sensitivity of 72% [51]; Coleman et al. reported a sensitivity of 62% and a speciftiy of 89% [52]; Cnossen et al. reported an average sensitivity of 37% and an average specifity of 89% similar to our results. This review included 8 studies with inconsistent definitions of high-risk patients. All of them rated persistent bilateral notching as pathological UtA Doppler and did not differentiate between early-onset and late-onset pre-eclampsia [37] (Table 2).

We obtained lower first-trimester PI-values than Lefebvre et al. when compared with their measurements at the level of the internal cervical os. When compared with their measurements at the crossover with the external iliac artery our results were comparable [43]. The overlap of the uterine artery PI values in pregnancies with and without pre-eclampsia changes significantly with gestational age, being far greater in the first trimester than later in the second trimester. This difference can be seen in the prognostic role in both the first and the second trimesters respectively.

Conclusion

Our results show, that the negative predictive value of uterine artery Doppler works well even in a high-risk group. Data however suggest relative poor positive predictive value of uterine artery Doppler even in a high-risk population using a cut-off of 2.5 PI. A value of the uterine artery Doppler using a high cut off might be in the significant increased specifity. A combination of maternal parameters, biomarkers and uterine artery Doppler seems to be essential and promising. The new risk model in early screening for pre-eclampsia developed by Akolekar et al. which combines maternal characteristics, mean arterial pressure, uterine artery PI, serum pregnancy-associated plasma protein-A and placental growth factor has been introduced at our clinic one year ago and the data will be published in an upcoming study [10].

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