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SCREENING FOR PREECLAMPSIA BY UTERINE ARTERY DOPPLER VELOCIMETRY IN THE LATE FIRST TRIMESTER OF PREGNANCY

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Abstract:

The Authors prospectively determined the uterine artery Doppler velocimetry (UADV) in 108 women with history of hypertensive disorder of pregnancy (HDP) between the 10th and 13th week of pregnancy to identify those at higher risk for recurrent preeclampsia and to evaluate the efficacy of prophylactic pharmacological treatment in this subgroup of patients. Patients with abnormal flow values (RI > 0.58 and any notching) were immediately started on aspirin 100 mg/daily, replaced by daily subcutaneous injection of low molecular weight heparin from the 24th week till delivery. Concerning the maternal morbidity (expressed by abnormal both mean blood pressure and 24-hour proteinuria throughout pregnancy), the Authors found that the average pregnancy course in 20 (18.5%) prophylactic treated patients with altered 1st trimester UADV (group A) was better than in their previous pregnancies, however regarding the above parameters no significant difference (P > 0.05) was found between the patients treated and another cohort of patients (n =20), also extrapolated from the same pool of patients at risk for HDP, but with normal I trimester UADV studies (group B) who were not prophylactic treated. Both groups of patients were followed up from the time of Doppler studies till 6 weeks post partum. The study suggests that UADV in the late first trimester of pregnancy is useful in reducing the risk of preeclampsia in patients with history of HDP, allowing the prompt institution of prophylactic treatment in selected patients.

1. Introduction

Preeclampsia (PE) is a multisystemic disorder that provokes a great number of maternal deaths worldwide. [1]

It is recognized as the 3rd cause of direct maternal mortality. PE risk factors are: elevated body mass index, maternal age extremes and Afro-American ethnicity; besides, some diseases such as diabetes and chronic hypertension also significantly increase the risk. [2-3]

Today it's well known that preeclampsia is a disease affecting the vascular endotelium.

A regularly evolving pregnancy is characterized by a preserved endothelial function and a progressive reduction in the resistance of uterine vessels, due to the placentation process. An inadequate

trophoblastic invasion and the consequent poor placentation are the key mechanisms of PE physiopathology. [4-7]

The systemic endothelial dysfunction, leading to thrombotic phenomenon in the microcirculation, reduces the perfusion of tissues and organs, including the placenta itself, creating an even more hypoxemic environment. Chronic placental hypoxia causes both oxidative stress with consequent placental apoptosis and necrosis and also an increased expression of proinflammatory, antiangiogenic, and angiogenic factors, amplifying the systemic endothelial impairment.

A good endothelial function and an optimal vascular dilatation are extremely important for a healthy gestation, without these conditions both maternal and fetal prognosis is compromised. [8]

According to the recent Literature [2], perinatal and maternal morbidity and mortality due to pre-eclampsia may be reduced through an early diagnosis and treatment.

Prediction of early pre-eclampsia (clinical symptoms before 34 weeks of pregnancy) is possible by searching for some circulating factors PAI (Plasminogen Activator Inhibitor) -1, Fibronectin, PlGF (Placental Growth Factor), VEGF (Vascular Endothelial Growth Factor) and other substances and/or by determining the uterine arteries Doppler velocimetry during the second trimester.

The use of UtA-PI alone in the second trimester of pregnancy allows detecting almost 95% of all cases of early PE [10], the uterine arteries bilateral notch is able to outline not only patients that subsequently develop PE, but also those whose pregnancies will be complicated by intrauterine growth restriction (IUGR). [11-12]

Determination of Doppler indices, during the late 1st trimester of pregnancy (from 11+0 to 13+6 gestational weeks) may be even more important in the management of pregnant patients with history of preeclampsia, [9] because it allows an earlier identification of an unbalance between proangiogenic substances, such as PlGF and others, and antiangiogenic factors, such as sVEGFR (Soluble Vascular Endothelium Growth Factor Receptor) -1 and others.

A part from the predictive value of the above circulating factors, there is no doubt that a lot of evidence in the Literature support an association between abnormal Doppler indices both in the I and II trimester of pregnancy and adverse pregnancy outcome especially in patient at risk. At this point a question raises spontaneously: what can the clinician do in the presence of abnormal UAD studies to improve pregnancy outcome, besides increasing maternal and fetal surveillance? A good number of medical treatments have been attempted in these cases with controversial results.

The aim of this study is not only to conduct a careful quantitative and morphological analysis of the pulsatile waves of uterine arteries in patients with history of HDP (Hypertensive Disorders in Pregnancy) and to eventually submit them to appropriate therapy, but also to evaluate the efficacy of such treatment.

2. Materials & Methods

The Authors did a prospective study using 2 cohorts of patients: A and B, extrapolated from a pool of 108 patients with history of hypertensive disorders in pregnancy (HDP), examined at the outpatient clinic of "Ospedale Santo Bambino" in Catania from January 2007 till December 2012.The patients' mean age and BMI (body mass index) were respectively 30 ± 0,4 years and 25 ± 0,2 kg/m2 ; all women underwent Doppler flowmetry of the uterine arteries between 10 and 13 weeks of pregnancy, using a 3.5 MHz multi frequency curvilinear

probe. The right and left uterine arteries were identified in an oblique plane of the pelvis at the crossover with the external iliac arteries and the Doppler signals were registered. The Doppler indices outlined, after the appearance of 3 similar consecutive waveforms, were: resistance index and any notching. Resistance index (RI) is defined as peak systolic flow minus end diastolic flow divided by peak systolic flow (A – B) / A. The diastolic notching is expressed by a characteristic waveform indicating decreased early diastolic flow in the uterine artery compared with later diastolic flow. The diastolic wave reduction, resistance index (RI) increase, the image of a "notch" between the systolic and diastolic components would be the expression of increased uterine resistance, which usually represents the first stage in the increase of peripheral resistance (fig.1, fig.2). The examination, if done by an experienced sonographer, is relatively simple and non-invasive, repeatable, and therefore it takes place in a very short time. An increased RI (> 0.58) and a characteristic unit and/or bilateral notch were found (tab. 3) in 20 patients (group A, tab. 1), 18,5 % of the total number of women examined, prenatal charts attesting mean B.P. and 24-proteinuria during the pregnancy complicated by the hypertensive disorder were obtained. Among the remaining 88 patients without flowmetric alterations, 20 patients with obstetrical history, age and BMI similar to group A patients, were selected and used as a control cohort defined as group B (tab. 2, 4). Group A patients were started to close clinical and ultrasound follow-up (every 15 days) for the assessment of fetal and maternal wellbeing from the late first trimester till delivery and treated with aspirin (100 mg daily) from the time of ultrasound examination to the 24th week, when they were switched to subcutaneous low molecular weight heparin (4.000 I.U. daily) till delivery and after. During the puerperal hospital stay and 6 weeks postpartum they were also re-evaluated for signs and symptoms of hypertensive disorders. Group B patients, although not subjected to any prophylactic treatment, were also followed up in the same manner as group A patients.

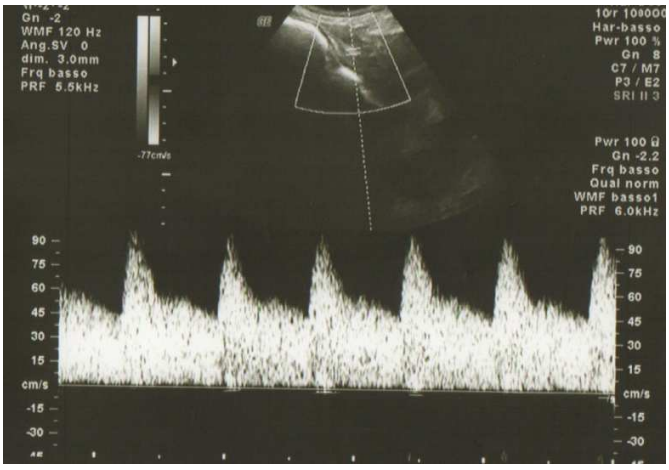

Figure 1. Normal uterine artery Doppler flowmetry

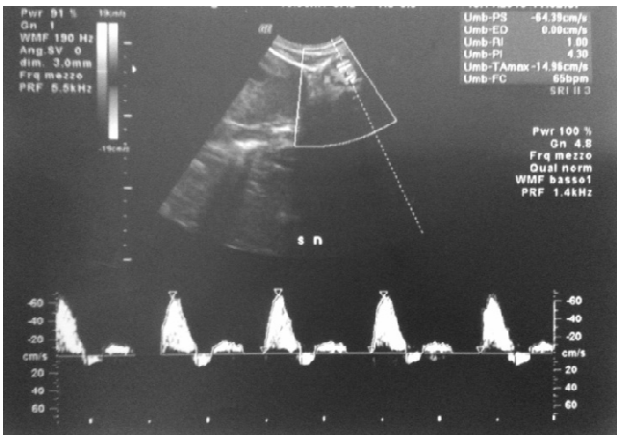

Figure 2. Abnormal uterine artery Doppler flowmetry

II and III trimester mean blood pressure and mean 24-hour proteinuria determined for each group A patient during the ongoing pregnancy were compared with those reported in the prenatal chart of the same patient during the previous pregnancy, the one complicated by the hypertensive disorder (Tab. 5).

The Authors also evaluated maternal and perinatal outcome regarding only the actual pregnancy in group B patients and related to both the previous and present pregnancy in group A patients.

Statistical analysis was carried out using t di Student test.

Table 1. Patient's characteristics (Group A)

	Age	Parity	BMI	Co morbidity	Previous HDP	Family History of Hypertension
1	32	1	28	hypothyroidism	X	Grandmother
2	26	2	20	--	X	--
3	30	1	24	--	X	--
4	28	1	23	--	X	--
5	38	3	28	--	X	Father and mother
6	24	1	19	--	X	--
7	30	1	26	Sinus tachycardia	X	Mother
8	29	1	28	--	X	--
9	35	2	28	--	X	--
10	40	3	30	Diabetes type I	X	Mother
11	33	2	23	--	X	--
12	26	1	24	--	X	Father and mother

13	28	1	22	--	X	--
14	32	1	29	--	X	Mother
15	32	2	22	Hypothyroidism	X	--
16	27	1	28	--	X	--
17	29	1	26	--	X	--
18	32	2	28	--	X	--
19	31	1	23	--	X	--
20	25	2	25	--	X	Sister

Table 2. Patient's characteristics (Group B)

	Age	Parity	BMI	Co morbidity	Previous HDP	Family History of Hypertension
1	30	1	25	--	X	--
2	32	2	28	--	X	Sister and mother
3	26	1	23	Hypothyroidism	X	--
4	28	1	22	--	X	--
5	24	1	30	--	X	--
6	36	2	24	--	X	Mother
7	30	1	25	Hypothyroidism	X	--
8	28	1	28	--	X	--
9	31	2	22	--	X	--
10	23	1	25	--	X	--
11	39	3	24	Diabetes type II	X	Mother
12	30	1	26	--	X	mother
13	28	2	25	--	X	
14	30	2	29	Hypothyroidism	X	Father and mother

15	29	1	21	--	X	
16	27	1	24	--	X	
17	32	3	26	--	X	Mother
18	29	2	25	--	X	
19	30	1	26	--	X	
20	31	2	24	--	X	Mother

Table 3. *Uterine artery flowmetric values (Group A)*

Patient	RI value
1	0,83
2	0,60
3	0,65
4	0,63
5	0,80
6	0,78
7	0,60
8	0,61
9	0,61
10	0,62
11	0,72
12	0,65
13	0,76
14	0,66
15	0,70
16	0,80
17	0,65
18	0,68
19	0,84
20	0,81

Table 4. *Uterine artery flowmetric values (Group B)*

Patient	RI value
1	0,58
2	0,50
3	0,55
4	0,53
5	0,50
6	0,48
7	0,50
8	0,51
9	0,51
10	0,52
11	0,52
12	0,55
13	0,48
14	0,56
15	0,52
16	0,55
17	0,51
18	0,48
19	0,53
20	0,54

Table 5. Previous pregnancy with HDP (Group A)

	II trimester		III trimester				
	Mean B.P.	Mean 24h Proteinuria (mg)	Mean B.P.	Mean Proteinuria (mg)	Term birth	Newborn weight (g)	Apgar
1	130/90	<300	160/90	550	36	2500	8
2	125/80	<300	145/90	350	37	2950	10
3	110/70	<300	145/95	400	37	3100	9
4	100/85	<300	140/80	<300	38	3000	9
5	130/80	<300	155/90	500	39	3300	10
6	120/85	<300	150/80	450	38	3025	10
7	125/90	<300	150/95	650	36	3120	10
8	110/70	<300	145/90	<300	38	3100	10
9	100/60	<300	150/90	500	38	2980	9
10	130/85	<300	160/95	650	36	2450	8
11	90/50	<300	145/90	450	38	3080	9
12	120/80	<300	150/90	500	37	3060	9
13	120/85	<300	150/85	450	39	3200	10
14	125/85	<300	145/90	450	39	3100	10
15	125/85	<300	145/90	400	39	3000	9
16	110/60	<300	140/100	800	36	2600	9
17	100/70	<300	150/90	500	38	3100	10
18	120/70	<300	145/95	550	37	3050	10
19	130/85	<300	160/90	700	36	2600	8

3. Results

All patients considered in group A had an excellent outcome both neonatal and maternal (blood pressure <130/90 mmHg and mean 24-h proteinuria < 300 mg throughout pregnancy), no cases of IUGR (intrauterine growth restriction) were reported, the mean neonatal weight being 3.100 ± 200 g with good Apgar scores.

Group A patients had a mean B.P. and a mean 24-hour proteinuria essentially normal and significantly lower, especially in the III trimester, than those registered during their previous pregnancy ($p < 0.05$; tab. 5-6), therefore in this group of patients the

average pregnancy course (in terms of maternal morbidity) was significantly better than before. Regarding patients of group B, 2 developed a mild degree of preeclampsia during the 34th week of pregnancy with a complete resolution 6 weeks post-partum (tab. 7).

The uterine artery RI (tab. 8) determination was repeated during the 24th week in both groups and decreased values were observed in 18 groups A patients (90%). No increased values were noticed in group B patients (tab. 9).

No significant difference in maternal morbidity was found between the patients treated and those (tab.4) with normal I trimester uterine artery Doppler flowmetry who were also followed till delivery but not prophylactic treated.

Similar overall perinatal outcome was observed between the two groups of patients and in group A patients between the present pregnancy and the previous one.

Table 6. Ongoing pregnancy with prophylactic treatment (Group A)

	II trimester		**III trimester**				
	Mean B.P.	Mean 24h Proteinuria (mg)	Mean B.P.	Mean Proteinuria (mg)	Term birth	Newborn weight (g)	Apgar
1	120/80	<300	120/80	<300	38	2500	8
2	125/80	<300	125/90	<300	39	2950	10
3	100/70	<300	125/80	<300	39	3100	9
4	100/70	<300	110/70	<300	39	3000	9
5	110/80	<300	120/80	<300	40	3300	10
6	120/75	<300	120/70	<300	39	3025	10
7	125/80	<300	125/70	<300	38	3120	10
8	100/65	<300	110/80	<300	39	3100	10
9	100/60	<300	120/80	<300	39	2980	9
10	110/75	<300	120/80	<300	38	2450	8
11	90/50	<300	100/70	<300	39	3080	9
12	120/80	<300	120/85	<300	39	3060	9
13	120/80	<300	120/80	<300	40	3200	10
14	125/70	<300	125/80	<300	40	3100	10
15	110/70	<300	120/60	<300	40	3000	9
16	110/60	<300	120/85	<300	39	2600	9
17	100/70	<300	110/70	<300	41	3100	10

18	120/70	<300	100/65	<300	39	3050	10
19	120/60	<300	120/80	<300	39	2600	8
20	120/75	<300	120/80	<300	38	2650	8

Table 7. Ongoing pregnancy without prophylactic treatment (Group B)

	II trimester		III trimester				
	Mean B.P.	Mean 24h Proteinuria (mg)	Mean B.P.	Mean Proteinuria (mg)	Term birth	Newborn weight (g)	Apgar
1	110/80	<300	120/80	<300	38	2900	9
2	95/60	<300	125/90	<300	39	3050	10
3	90/50	<300	125/80	<300	39	3200	10
4	120/80	<300	170/100	650	36	2005	8
5	100/70	<300	120/80	<300	40	3400	10
6	110/70	<300	120/70	<300	39	3125	10
7	105/60	<300	125/70	<300	38	3320	10
8	120/85	<300	160/100	500	37	2100	8
9	100/60	<300	120/80	<300	39	2980	9
10	110/70	<300	120/80	<300	38	3450	9
11	110/75	<300	100/70	<300	39	3180	9
12	120/80	<300	120/85	<300	39	3260	9
13	120/85	<300	120/80	<300	39	2850	8
14	110/80	<300	100/70	<300	40	3100	9
15	120/80	<300	125/80	<300	40	3200	9
16	110/70	<300	120/70	<300	40	3470	10
17	100/60	<300	110/70	<300	41	3520	9
18	110/70	<300	110/80	<300	41	3050	10
19	100/50	<300	120/80	<300	40	3210	10
20	120/70	<300	120/80	<300	41	3190	10

Table 8. Uterine artery flowmetric values at 24th week during therapy (Group A)

Patient	RI value
1	0,80
2	0,57
3	0,55
4	0,56
5	0,58
6	0,57
7	0,55
8	0,54
9	0,52
10	0,58
11	0,57
12	0,67
13	0,57
14	0,55
15	0,58
16	0,57
17	0,51
18	0,52
19	0,53
20	0,54

Table 9. Uterine artery flowmetric values at 24th (Group B)

Patient	RI value
1	0,57
2	0,51
3	0,55
4	0,54
5	0,52
6	0,50
7	0,52

8	0,50
9	0,51
10	0,52
11	0,50
12	0,55
13	0,49
14	0,57
15	0,51
16	0,55
17	0,51
18	0,49
19	0,50
20	0,54

4. Discussion and Conclusion

This study has shown that a significant proportion of patients (18.5%) with HDP risk have an abnormal uterine artery Doppler velocimetry early in pregnancy and that uterine artery flow determination in the late first trimester of pregnancy may be useful in reducing the risk of preeclampsia allowing the prompt institution of prophylactic treatment and increased maternal fetal surveillance. What is the best treatment protocol is still uncertain. The one proposed in this paper seems to work very well. Certainly other studies are necessary to confirm these results.

Another argument still controversial is what is the best uterine artery Doppler index, to be used alone or in combination with others, in predicting an adverse pregnancy outcome. The presence of a bilateral notch should be considered highly predictive of subsequent preeclampsia (RR = 21.99, sensitivity 92.9%, specificity 85.1%) at early gestational age (10-13 weeks), as well as at 24th week (sensitivity 81.2%, positive predictive value 27%). [13] However, using a RI cut-off of > 0.58, a higher predictive value of 70% is reached, but with a lower sensitivity (63%).

The early measurement of the arcuate arteries resistance could, therefore, reveal an impaired trophoblastic invasion of the uterine arteries, holding a high predictive power, and offering the possibility to evaluate the uterine and fetal district longitudinally, by monitoring the effects of the disease over time.

Concerning the combination of Doppler indices with dosage of serous maternal factors, in Literature there are various data that are discordant from each other.

Some Authors says that UADV and maternal serum PlGF (Placental Growth Factor) estimation at 20-22 weeks of gestation are strong predictors of the occurrence of pre-eclampsia when used individually but together their association with pre-eclampsia is not significant. [14]

Other Authors, on the other side, assert that in models using maternal history and 11-14 week-UADV, the negative predictive value of the test is high, while abnormal UADV may identify an equally high proportion of women that will develop early-onset

preeclampsia. Besides, they believe that algorithms combining biochemical markers could still improve the prediction rate at higher cost and complexity; [15] for instance, according to some researchers, the only determination of maternal plasma PAI-1 combined with fibronectin seems to have the highest predictive value for preeclampsia. [16]

In conclusion maternal history should guides the clinician if whether or not administering a specific predictive protocol for preeclampsia to a patient, the use of ultrasonography of the uterine artery either alone or in combinations with the dosage of specific maternal factors should be reserved to high risk patients. UADV does not seem helpful in the low risk pregnant population.

Although the present study is based on a restricted number of patients, it does show that patients at risk for PE with abnormal UADV benefit from prophylactic treatment, which has a significant impact on maternal morbidity without affecting the overall maternal and perinatal outcome.

Probably, by selecting larger number of patients, prophylactic treated and not, the observed reduction in maternal morbidity could also affect maternal and perinatal long term morbidity and mortality.

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