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**The transcranial Doppler of maternal cerebral arteries
and the prediction of pre-eclampsia**

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Abstract

Background: Pre-eclampsia is a major cause of maternal and perinatal death. Parameters derived from the Doppler waveform in different vascular beds have been studied as possible predictors of pre-eclampsia.

Objectives: To assess whether second –trimester changes in transcranial Doppler parameters of normotensive pregnant woman are associated with the subsequent development of pre-eclampsia.

Search Strategy: The strategy for identification studies was based on the search performed in electronic databases. In addition, reference lists of retrieved articles were checked.

Selection Criteria: We selected all case-control and cohort studies providing measures of cerebral arteries parameters by transcranial Doppler among normotensive women in the second-trimester of pregnancy.

Data collection and analysis: We assessed studies for methodological quality, according to the Critical Appraisal Skills Programme. One reviewer assessed the studies for inclusion and extracted data. The outcome we sought was the occurrence of pre-eclampsia / eclampsia.

Main Results: Three studies involving 485 women were included. Considering the heterogeneity of data a meta-analysis of these was considered not feasible. One cohort study observed that the maternal middle cerebral artery blood flow velocity assessed by transcranial Doppler did not show any ability to predict the occurrence of pre-eclampsia. One case-control study observed that the middle cerebral arteries pulsatility and resistance indices were lower in the second trimester in the women who later would develop pre-eclampsia. Another case-control study did not corroborate this predictive capacity.

Reviewers' conclusions: Further research is needed to define the ability of transcranial Doppler in the prediction of pre-eclampsia. Until further evidence is available, the transcranial Doppler may not be performed to predict or promote the earlier detection of pre-eclampsia.

Background

The pre-eclampsia is a multiorganic disease, responsible for a significant number of maternal and perinatal deaths all over the world (SIBAI, 2005). Pre-eclamptic women frequently present cerebral involvement, which is attributed to pathological vascular alterations, mainly affecting the parietal and occipital lobe (HORN, 1990; RICHARDS, 1988). Nevertheless, any pregnant woman experiences several physiological adaptations, including changes in the cerebral hemodynamics, and the major part of the information about these cerebral changes has been obtained from cross-sectional studies or studies with small animals. (WILLIAMS, 2003; BELFORT, 2001).

The relative paucity of data on this topic is attributed to technical and ethical constraints. However, the introduction of the transcranial Doppler in the clinical practice is considered by some researchers as a possibility to assess the cerebral state during the pregnancy (BELFORT, 2001; WILLIAMS, 2003)

The transcranial Doppler is a non-invasive method, able to measure direct parameters (cerebral blood flow velocity) and indirect parameters (pulsatility index, resistance index, and cerebral perfusion pressure) of the cerebral hemodynamics. (BELFORT, 2001). Indirect parameters are used because there are some situations (i.e. vasospasm), where the blood flow velocity and the blood volume vary in opposing directions, and, consequently, the assessment of the cerebral perfusion is not appropriate using only absolute values of blood flow velocity (BELFORT, 2001). Because of this reason, in clinical practice, it has been proposed the use of the pulsatility index and the resistance index, whose measurement are not influenced by the insonation angle. These indirect parameters confer additional advantage in the evaluation of the cerebral perfusion in studies where multiple measures of the same subject are necessary (Riskin-Mashiah, 2002)

Studies evaluating parameters derived from the Doppler waveform in others vascular beds shown some ability to predict the development of pre-eclampsia (AUBIBERTI, 2005; PERINI, 2004; FLORIO, 2005). This review will attempt to evaluate the second-trimester changes in transcranial Doppler parameters as a predictive factor of the subsequent development of pre-eclampsia.

Objectives

The aim of this review is to assess whether second –trimester changes in transcranial Doppler parameters of normotensive pregnant woman are associated with the subsequent development of pre-eclampsia.

Criteria for selecting studies

Types of studies

To assess whether second-trimester changes in transcranial Doppler parameters can be associated with the subsequent development of pre-eclampsia, all case-control and cohort studies providing measures of the above cited parameters among normotensive women in the second trimester of pregnancy were considered.

Types of participants

Any normotensive pregnant woman in the second trimester of pregnancy. Women with chronic hypertension or high blood pressure in the first trimester were excluded.

Types of outcome measures

For all women: pre-eclampsia / eclampsia.

Search strategy

We searched for published studies reported between 1994 and 2004 in any language. The strategy for identification studies was based on the search performed in electronic databases (Medline, Popline and SciELO). In addition, reference lists of retrieved articles were checked.

Methods of the review

One reviewer assessed the eligibility of identified citations on the basis of the titles and / or abstracts. The citations considered irrelevant were excluded. If the information provided by titles or abstracts was considered insufficient to decide on the inclusion or exclusion, the full-text was retrieved and evaluated. All citations, whose titles or abstracts were considered relevant to the review, the full-text was also retrieved and evaluated.

A quality appraisal of the included studies has been performed, according to the Critical Appraisal Skills Programme (CASP).

Description of studies

Moutquin (1999) studied a cohort of 395 normotensive primiparous women. The maternal blood flow velocity in the middle cerebral artery was assessed at 20-24 and 28-32 weeks of gestation, in the left lateral recumbence position and in the sitting position with the head of the bed raised to 90°.

Riskin-Mashiah (2002) performed a nested case-control study, with 10 preeclamptic women and 20 normotensive pregnant women. Each case was matched for gestational age at the time of initial examination, maternal age and parity with two controls. The measurement of cerebral velocity parameters was performed in the left lateral position, with and without maneuvers to test the vascular reactivity of the middle cerebral arteries (5% carbon dioxide inhalation and a two minute isometric handgrip test).

Williams (2004) performed a nested case-control study with 20 preeclamptic women and 40 normotensive pregnant women. Each case was matched with two controls for maternal age. The middle cerebrovascular Doppler parameters were assessed at 20-24 weeks and 28-32 weeks of gestational age, in the sitting position with the head of the bed raised to 90°.

Methodological quality of the included studies

Moutquin (1999): The description of the methods is scanty. There is paucity of data regarding the recruitment process, the measurement of the cerebral blood flow velocity and the identification of the outcome.

Riskin-Mashiah (2002): The cases and the eligibility criteria are precisely defined. The sample size was not computed but based on the length of the study, resulting in a very small sample. The matching process addressed the main confounding factors, but the chosen ratio of case :control (1:2) determined a small sample of controls. The methods applied to measure the cerebral blood flow velocity are detailed but the number of examiners was not stated. The authors have taken account of the main potential confounding factors in the design but the woman's smoking status was not declared.

Williams (2004): The cases are precisely defined but the eligibility criteria were not clear. The sample size was not computed a priori. The matching process addressed only the maternal age. The methods applied to measure the cerebral blood flow velocity are detailed but the number of examiners was not stated.

Results

Moutquin (1999): It was observed that five percent of the cohort developed pre-eclampsia. The maternal middle cerebral artery blood flow velocity was similar in the second and third trimester in both groups.

Riskin-Mashiah (2002): The middle cerebral arteries pulsatility and resistance indices were lower in the second trimester in the women who later would develop pre-eclampsia. The maneuvers to

test the vascular reactivity of the middle cerebral artery have shown a reduction of resistance and pulsatility indices in both groups, but without significant differences between the groups.

Williams (2004): The blood flow velocity and the pulsatility index did not differ in the second or third trimester between the case and the control groups. It was observed a significant prolongation in the percentage of the end systolic time at the 28th gestational week in the case group, but at this time the mean arterial blood pressure already significantly elevated.

The characteristics of included studies are shown in table 1. Considering the heterogeneity of data a meta-analysis of these three studies was considered not feasible, but a summary of the results is shown in the table 2.

Discussion

A number of previous studies evaluating parameters derived from the Doppler waveform in different vascular beds have been performed to study the ability to predict the development of pre-eclampsia. One cohort and two case-control studies have addressed the assessment of middle cerebral artery by transcranial Doppler as a predictory way to predict pre-eclampsia.

Nevertheless, in these studies, there were methodological problems, that can affect the reliability of the results. For example, in the case-control studies, the controls' capacity for representing the population that generated the cases is uncertain, considering its reduced number. Another possible problem is the occurrence of measurement bias, once that none of the three studies declared the number of examiners performing the transcranial Doppler, and none of them mentioned any control of the inter and intra-examiner variability. The smoking status of the women in any study was not clarified.

Pre-eclampsia is a major problem in the field of reproductive health. Developing strategies to allow its early detection, ideally before its clinical manifestation, must remain as a goal to researchers dealing with this topic. However, considering the available data, the ability of transcranial Doppler in the prediction of pre-eclampsia is still uncertain.

Reviewer's conclusion

Implications for practice

Until further evidence is available, the transcranial Doppler may not be performed to predict or promote the earlier detection of pre-eclampsia.

Implications for research

Further research is needed to define the ability of transcranial Doppler in the prediction of pre-eclampsia. Future studies should include larger samples and address the inter- and intra-examiner variability.

Table 1: Characteristics of included studies

Study	Design	Participants	Sample Size	Outcome
Moutquin (1999)	Cohort	Inclusion Criteria: Normotensive Pregnant Women at the Second Trimester of Gestation	395 Women	Occurrence of Pre-eclampsia
Riskin-Mashia (2002)	Case-Control	Inclusion Criteria: Normotensive Pregnant Women at the Second Trimester of Gestation Exclusion Criteria: Chronic hypertension, Women with twin pregnancy, women who were using vasoactive medications, and women with vascular disease or other chronic conditions	10 cases and 20 controls	Occurrence of Pre-eclampsia
Williams (2004)	Case-Control	Inclusion Criteria: Normotensive Pregnant Women at the Second Trimester of Gestation	20 cases and 40 controls	Occurrence of Pre-eclampsia

Table 2: Maternal middle cerebral artery parameters assessed by transcranial Doppler at the second trimester of gestation

Study	<u>Women who remained normotensive</u>				<u>Women who latter developed pre-eclampsia</u>			
	n	CBFV	Pulsatility Index	Resistance Index	n	CBFV	Pulsatility Index	Resistance Index
Moutquin (1999)	375	60.3 ± 10.4	-	-	20	63.7 ± 8.0	-	-
Riskin-Mashia (2002)	20	-	0.83 ± 0.03*	0.54 ± 0.01**	10	-	0.73 ± 0.03*	0.50 ± 0.01**
Williams (2004)	40	66.46 ± 1.2	1.05 ± 1.9	-	20	69.25 ± 14.7	1.92 ± 0.21	-

* and **= p<0.005

CBFV: Cerebral Blood Flow Velocity

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