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Notch depth index alone and in combination with pi in prediction of preeclampsia at or before 32 weeks of pregnancy

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1. Introduction

Preeclampsia remote from term (onset at or before 32 weeks of pregnancy) is one of the major obstetric vasculopathies. Obstetric vasculopathies are all those obstetric conditions that have a placental vascular origin. These include – recurrent spontaneous missed miscarriages of late first trimester and early second trimester, preeclampsia remote from term, IUGR, Recurrent Still-births and accidental hemorrhage [1]. Adverse maternal and fetal outcome is more consistent with preeclampsia remote from term than with preeclampsia that has a clinical onset after 32 weeks of pregnancy. As the treatment of its cause remains elusive, its prediction is much sought after. Most of the studies use a combination of at least two parameters to predict preeclampsia. Also, in most of these studies, one parameter is biochemical. Of late uterine artery Pulsatility Index (PI), Mean Arterial Pressure (MAP) and Pappalysin-1, also known as Pregnancy-Associated Plasma Protein A (PAPP-A) are popularised in the prediction of preeclampsia following research papers published by workers in Fetal Medicine Foundation of UK [2]. It has been found that such a combination of parameters is more accurate in predicting preeclampsia [3]. A practical difficulty that arises in including a biochemical parameter is the need for an extra agency, in this case being a pathology laboratory. Also, in a setup like that of this study, where the pregnant subject has to bear all costs, it entails extra burden on her personal resources. It was therefore envisaged to find a method which does not need an extra visit to the laboratory and does not invite an extra burden on the financial resources of the pregnant subject. At the same time, the method has to be effective in its function of prediction of preeclampsia.

In this original prospective longitudinal study, we have researched the competence and efficacy of tools that may help in predicting preeclampsia remote from term without the need for any biochemical testing. For this purpose, we have studied the color Doppler parameter, Notch Depth Index (NDI), singly and in combination with PI $>$ 1.7, in the prediction of preeclampsia remote from term. NDI is calculated as described by Takahashi et al. [4]. It is detailed in the subsequent section of Materials and Methods.

NDI is being seen as a useful marker for one important reason. It doesn't need a different technology platform like a laboratory study. Also, NDI is an index of resistance offered to the blood flow in the spiral arterioles in early pregnancy. More the resistance offered to the blood flow, deeper the notch. This gets directly reflected in the index of the notch – NDI. Blood and other lab parameters are based on allied phenomena that are occurring with preeclampsia. NDI is based directly on the behaviour of vascular resistance in the uterine artery flow.

There is an inherent simplicity in measuring this index. All that is required is to place the cursor of the USG machine at the four points shown and for calculating the index (as shown in Fig. 1). After this all that one needs is the simple calculator. It is possible that initially one may find it to be one step more in the 11–14 weeks scan of pregnant subjects. But in the advantages that it offers and the simplicity and logistic benefit that it has, this index has the potential to prove to be a very useful index in prediction of preeclampsia.

If this tool works well only the single imaging technology can be competent enough in the prediction of preeclampsia remote from term.

2. Materials and methods

This is a prospective study commencing from the first enrolment at first trimester right to their obstetric outcome. This was done clinically and through uterine artery color Doppler. They were observed specifically for the development of preeclampsia at or before 32 weeks (aka preeclampsia remote from term). The population screened was at a midlevel obstetric care unit which predominantly cares for urban population. Subjects were screened irrespective of the risk for preeclampsia. This was a part of routine screening programme for subjects attending the hospital for antenatal care.

Enrolled pregnant subject was labelled as preeclamptic if she developed hypertension after 20 weeks of gestation with previously normal BP with or without proteinuria. Hypertension of preeclampsia was labelled following standard norms as a BP of 130 systolic and/or 90 diastolic in pregnancy taken on two consecutive readings six hours apart after adequate rest of at least half an hour [5]. Proteinuria was detected through standard dipstick test.

Color Doppler was done with GELOGIQ F8 ultrasound machine. For

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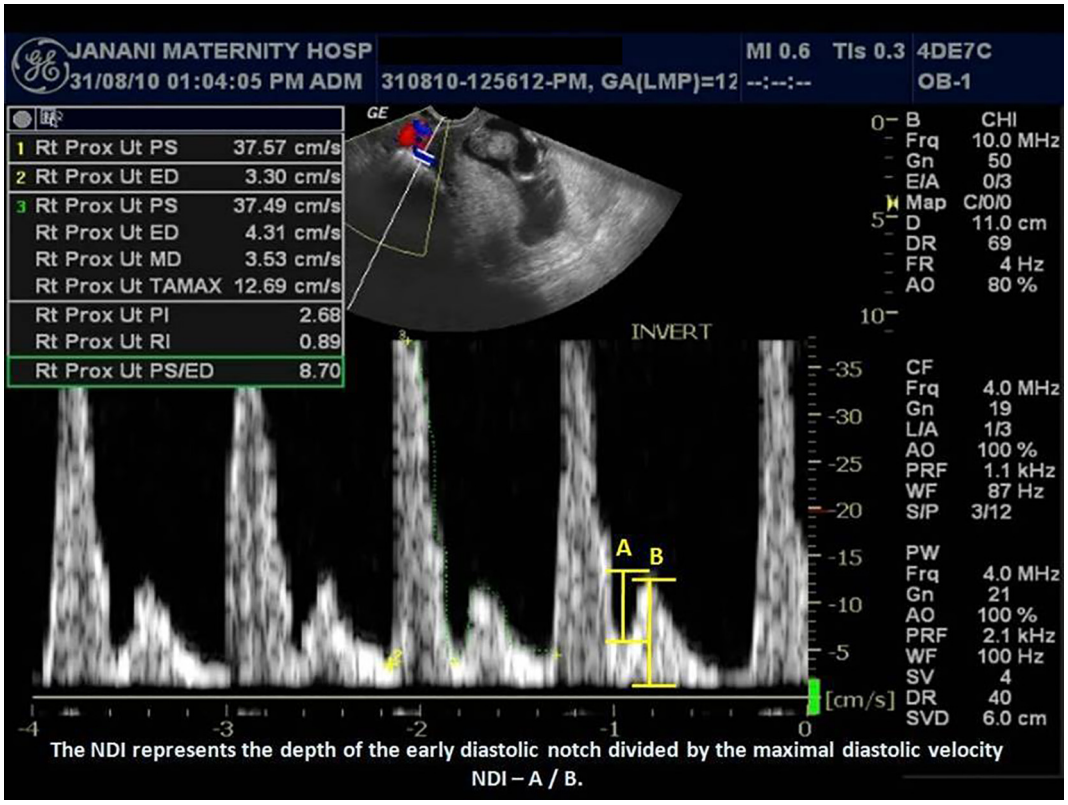

Fig. 1. Calculation of NDI.

this study, only first trimester scan between 11 and 13 weeks of pregnancy was required. All scans were performed by the author. It was done by transvaginal route. Using Doppler ultrasound, the main branch of the uterine artery could be easily located at the cervicocorporeal junction. With the help of real-time color imaging, Doppler velocimetry measurements were performed by standard and well-established methods [6]. Transvaginally, the probe was placed in the anterior fornix. A midsagittal section of the uterus was obtained and the cervical canal was identified. The probe was then moved laterally until the paracervical vascular plexus was seen. Color Doppler was then turned on and the uterine artery was identified as it turns cranially to make its ascent to the uterine body. Measurements were taken at this point before the uterine artery branched into the arcuate arteries.

2.1. Calculations of indices were done as follows

NDI was calculated as recommended by Takashaki et al. [4] in which the depth of early diastolic notch was divided by the maximum diastolic velocity. This has been made clear in Fig. 1

The results of these calculations become more clear in Figs. 2 and 3. NDI of this subject of Fig. 2 was 0.371 and that shown in Fig. 3 was 0.121.

PI or Pulsatility Index was calculated as Peak Systolic Velocity minus The End Diastolic Velocity divided by Time-Averaged Velocity = (PSV − EDV)/TAV. These values were readily provided by the sonography machine itself.

The value of 0.55 for NDI was reached using the statistical tool of regression analysis. Figure pf 1.7 for uterine artery PI in first trimester scan was used on basis of many standard publications on this, two typical ones being [7,8]. Both variables studied, NDI and PI are independent variables totally not related to each other. NDI is independent of uterine artery PI. Therefore what affects uterine artery PI may not necessarily affect NDI.

All enrolled subjects were serially followed up to delivery and their obstetric outcome noted especially for the development of preeclampsia. Those subjects whose obstetric outcome could not be recorded for whatever reason were excluded from the study.

2.2. Statistical analysis

The data so obtained from the study was subjected to statistical analysis. Diagnostic test evaluations were done using MedCalc's online Diagnostic test statistical calculator includes Sensitivity, Specificity, Likelihood ratios, Predictive values with 95% Confidence Intervals. Chi-square test was used to analyze the statistical significance with statistical significance was estimated as $P < 0.05$. The results so obtained were examined in light of available references.

3. Results

There were 229 prospectively followed up subjects who had NDI > 0.55. They were analysed for a possibility of developing preeclampsia remote from term. Distribution of these subjects in reference to the development of preeclampsia is shown in Table 1. It was found that those subjects who had NDI > 0.55, had a statistically significant chance of developing preeclampsia remote from term.

As shown in Table 2, the Chi-square value was 22.8233, with a P value less than 0.05, making it statistically significant. It had a sensitivity of 43.48% and a specificity of 87.36%. Both values were well within 95% CI and the false positive rate was 10.08%. Other statistical results are also shown in the table.

So as to eliminate the possibility of the inefficiency of using a single parameter in predicting preeclampsia, NDI > 0.55 was combined with one more tool, a PI > 1.7 and examined for the possibility of developing preeclampsia. There were 123 subjects in this group. Distribution of these subjects with NDI > 0.55 and PI > 0.17 in reference to the development of preeclampsia is shown in Table 3.

It was found that those subjects who had NDI > 0.55 and

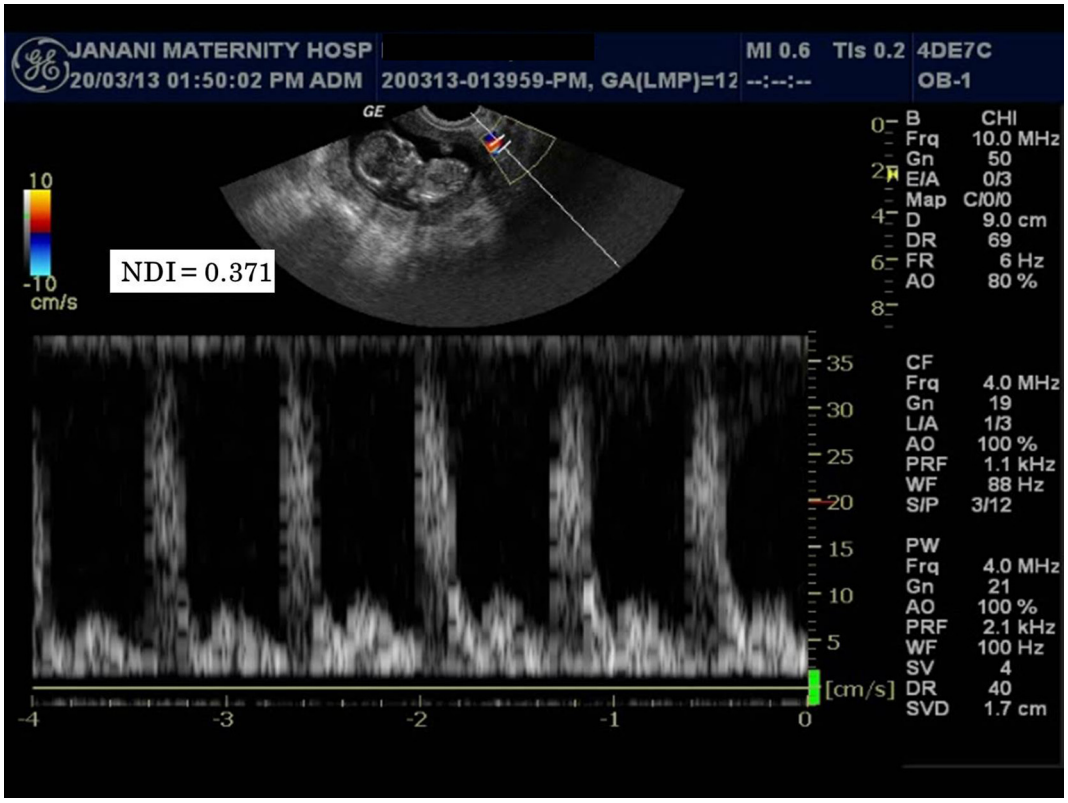

Fig. 2. NDI = 0.371.

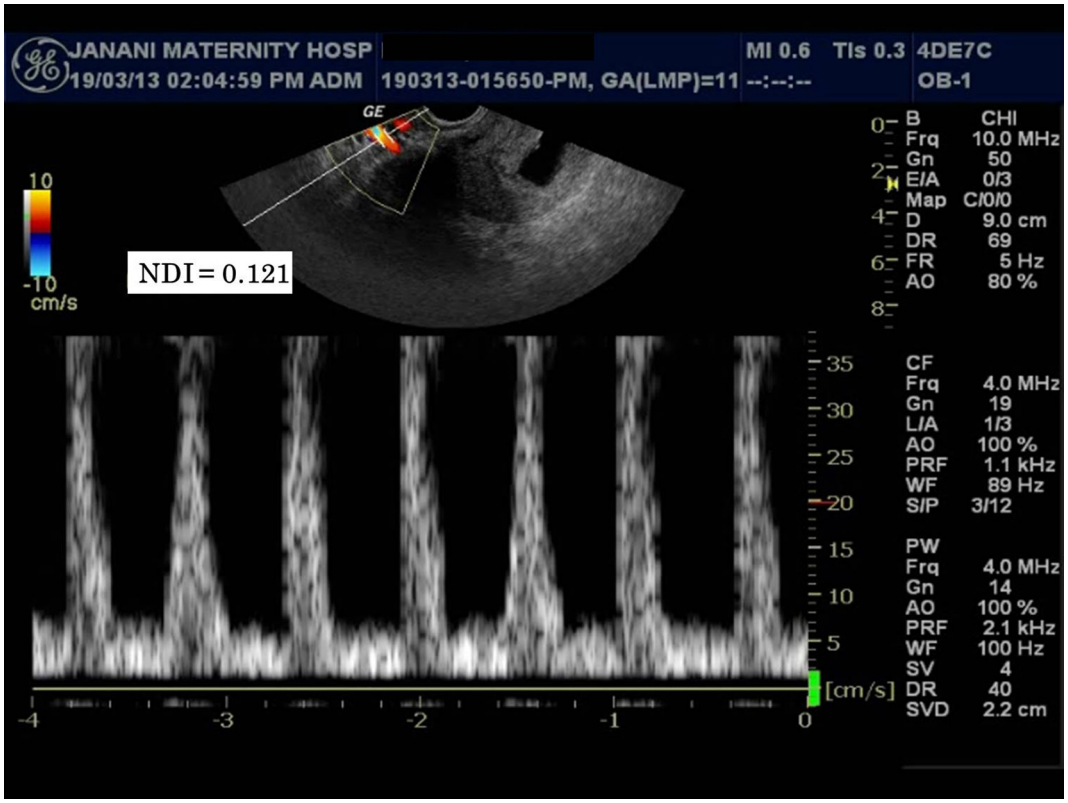

Fig. 3. NDI = 0.121.

Table 1
NDI.0.55 and preeclampsia (N = 228).

NDI > 0.55 and PIH	True positive	20
NDI < 0.55 and no PIH	True negative	159
NDI > 0.55 and no PIH	False positive	23
NDI < 0.55 and PIH	False negative	26

False Positive = 10.08%.

Table 2
Statistical analysis of Table 1.

Statistic	Value	95% CI
Sensitivity	43.48%	28.93–58.89%
Specificity	87.36%	81.64–91.82%
Positive Predictive Value	46.51%	34.43–59.02%
Negative Predictive Value	85.95%	82.51–88.80%
Chi-square	22.8233	**significant at p < .05**

Table 3
NDI.0.55 and PI > 1.7 and preeclampsia (N = 123).

NDI > 0.55 PI > 1.7	True positive	17
NDI > 0.55 PI < 1.7	True negative	76
NDI < 0.55 PI > 1.7	False positive	18
NDI < 0.55 PI < 1.7	False negative	12

False Positive = 14.6%.

Table 4
Statistical analysis of Table 3.

Statistic	Value	95% CI
Sensitivity	58.62%	38.94–76.48%
Specificity	80.85%	71.44–88.24%
Positive Predictive Value	48.57%	36.06–61.27%
Negative Predictive Value	86.36%	80.24–90.81%
Chi-square	16.9611	**significant at p < .05**

PI > 1.7, had a significant chance of developing preeclampsia. As shown in Table 4, the Chi-square value was 20.1361, with a P value < 0.05, making it statistically significant. It had a sensitivity of 58.62% and a specificity of 80.85%. Both values were well within 95% CI. Other statistical results are also shown in the table.

4. Analysis and discussion

This prospective study shows that a PI value of 1.7 or more when combined with NDI of 0.55 at first trimester (11–13 weeks) scan is competent in predicting preeclampsia in singleton pregnancies.

Preeclampsia remote from term is an obstetric vasculopathy. It is therefore prudent to study changes in relevant vessels to know the intricacies of this condition. It is proved that Color Doppler is the most discriminative for predicting both early preeclampsia and early preterm birth [9]. With the introduction of ultrasonography especially color Doppler in the clinical practice of obstetrics, the face of screening for preeclampsia has completely changed. PI > 1.7 is considered as having a good value for prediction of high-risk subjects for preeclampsia [10]. When diligent research scientists in this field take a bird's eye view of the screening tests, one fact becomes obvious. A single test is not as competent as a combination of tests in predicting preeclampsia efficiently. In this study, we have used NDI alone and in combination with PI > 1.7 to predict preeclampsia.

11–13 weeks USG scan is now routinely performed in pregnant subjects for gaining much information. It is a very well-known fact that the second wave of trophoblastic invasion plays a very important role in the causation of preeclampsia remote from term and other obstetric vasculopathies. This second wave of trophoblastic invasion completes by the second trimester in normal pregnancies. However, when the first trimester scan is usually performed (11–13 week), the second wave of trophoblastic invasion is still incomplete and is manifested as a diastolic notch (also expressed as a pre-diastolic notch in some literature) on uterine artery color Doppler study. Interestingly, the depth of this diastolic notch seems to be holding a good promise in the prediction of preeclampsia.

11–13 weeks was used in this study for performing the study as that is the time when all subjects coming for antenatal care are subjected to first trimester sonographic scan across the globe. Also, if at this scan if pregnant subjects who are high-risk for development of preeclampsia are competently identified, preventive measures like low dose aspirin (LDA) can be started now.

There are not many references of NDI in literature as this is one of its kind study. Takahashi K and others studied NDI a little later in the pregnancy [4] at 16–18 weeks. The present study uses NDI at 11–13 weeks. At 16–18 weeks starting LDA may not be of much help to the pregnant subject if found to be high-risk. Therefore obviously sooner the better and so 11–13 weeks – the usual time for the first trimester scans in all pregnant subjects who come for regular antenatal care.

It has been found in this study that the combination of uterine artery PI and NDI, at 11–13 weeks scan is effectively able to predict preeclampsia without the need of doing any biochemical markers. Doing a biochemical marker involves a different agency and in most parts of the world is to be paid separately by the pregnant subject from her personal resources. Both these indices that are studied here in combination, eliminate the need of doing the biochemical marker. As a result the cost reduces, the time spent in getting biochemical tests done is eliminated and the hassle for the pregnant subject of going to two agencies, sonography and laboratory is reduced.

Screening for the development of preeclampsia is provided in the first trimester of pregnancy when USG scans are performed between 11 and 13 weeks. Usually, these screening methods use a combination of maternal risk factors, uterine artery Doppler, mean arterial pressure, maternal serum PAPP-A, and placental growth factor. They have been able to identify about 95% of cases of preeclampsia on or before 32 weeks of pregnancy for a false-positive rate of 10% [2]. Results of the present study are well comparable to the referred studies. NDI singly and in combination with PI > 1.7 shows a robust statistical significance, a sensitivity, and specificity well within the 95% confidence interval (CI) and a false positive rate of around 10%.

One principal advantage of this study is the fact that it can eliminate the need for laboratory testing of blood markers like PAPP-A or Placental Growth Factor (PGF) and others. The entire screening template can be completed in one single ultrasound study. This makes the present method convenient to use and therefore easy to apply.

As regards the limitations of the study, for performers of sonography, calculating an additional parameter using a calculator may be perceived as cumbersome. In some cells of the tables of results, the number of subjects may be considered less and therefore more subjects over a period of time can strengthen the results all the more.

5. Conclusion

Notch Depth Index of 0.55 or more at 11–13 weeks scan alone and in combination with PI > 1.7 is a good tool for prediction of early-onset preeclampsia (occurring at or before 32 weeks) without the need of any laboratory tool.

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