Fetal middle cerebral artery Doppler in post term pregnancy: a predicting factor for induction of labor outcome

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Abstract

Background: Post term pregnancy necessates IOL to avoid the potential hazards on fetal and maternal outcome. Several factors affect the process of IOL, and there is often great uncertainty regarding its success. Late in pregnancy, vasodilatation of fetal brain vessels occurs as a physiological preparation for the onset of labor. MCA-PI decreases in turn as a preliminary fetal mechanism for adaptation to labor.

Objective: We assumed that evaluating MCA-PI prior to IOL may be used as a beneficial tool to predict responders to IOL.

Methodology: A prospective cohort study, which included 150 post term patients (41-42 weeks), who were admitted to Kasr Al-Ainy Hospital for IOL. Prior to induction, we performed U/S to record MCA-PI, together with CL and EFW. Patients were given 25Mcg misoprostol vaginal tab/6 hours, maximum for 24 hours. Responders were defined as those who succeeded to enter the active phase of labor, by the onset of active uterine contractions. Patients who needed CS before the onset of active labor were excluded.

Results: A total of 150 patients were included in the study. 133 cases (88.7%) entered the active phase of labor, while 17 (11.3%) cases failed to enter in the active phase. Both groups were comparable in the parity and BMI. MCA-PI was significantly lower in the responder group (group 1; 1.29± 0.11) compared to the non-responders (group 2;1.67± 0.13). The mean CL was 25.28± 4.25 & 33.43± 4.8 in groups 1&2 respectively. The mean EFW was 3375.47± 178 & 3722.65± 116.33 in groups 1 & 2 respectively. ROC analysis examined the ability of these parameters in predicting the response to IOL. The cutoff values, sensitivity & specificity respectively were; 1.41, 94.12% , 83.46% for MCA-PI, 26.6, 94.1%, 60% for CL, and, 3555, 94%,83.5% for EFW. WE further included all significant variables (maternal age, MCA-PI, CL, EFW) in a multivariate logistic regression analysis. MCA-PI was a statistically significant predictor for the response to IOL, even after adjustment of the other variables (P value= 0.05).

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Conclusion: MCA-PI evaluation prior to IOL is a useful tool in prediction of IOL outcome. Lower PI values may predict successful outcome. CL assessment and EFW are other factors that may predict the outcome of IOL.

KEYWORDS: post term pregnancy, MCA-PI, induction of labor, outcome

Introduction

Post term pregnancy imposes a great risk on fetal outcome, with increased perinatal morbidity and mortality. Moreover, it is associated with higher rates of cesarean sections, postpartum hemorrhage, and the need for induction of labor (IOL) (1, 2).

Taking into consideration both maternal and fetal potential risks, IOL as pregnancy advances beyond 40 weeks, seems to be the current best practice (3, 4). Still, it is quite challenging for the obstetrician to determine those who will adequately respond to IOL.

There are several factors affecting IOL, such as; parity, body mass index (BMI), fetal weight. Many parameters have been proposed by different researchers to predict the outcome of IOL; Bishop score in the 1960's (5), cervical length assessment (6, 7, 8), and more recently, posterior cervical angle measurement (9, 10, 11) and cervical elastography (12).

In the last weeks of gestation, vasodilatation of the fetal brain vessels occurs as a physiological preparation for the onset of labor. In turn, the fetal middle cerebral artery -pulstility index(MCA-PI) decreases preceding the onset of labor, as a preliminary fetal mechanism for adaptation to labor (13,14).

Since there has been an association between MCA Doppler changes and the onset of spontaneous labor (13), we assumed that evaluating MCA-PI prior to IOL may be used as a beneficial tool to predict responders to IOL.

Materials and Methods

This is a prospective cohort study, including 150 pregnant patients in late term pregnancy, who were admitted to Obstetrics and Gynaecology Department, Kasr El-Aini Hospital, Cairo University, for IOL, from March 2019 to March 2020, after approval of our ethical committee.

Before enrollment in the study, thorough history taking and clinical examination were done to verify the fulfillment of the inclusion criteria; having a singleton, living fetus, cephalic presentation, with a gestational age (GA) range; 41 to 42 weeks (as evident by reliable dating from the last menstrual period, or first trimesteric ultrasound), intact membranes and favorable cervix on examination (Bishop score >6). Cases with BMI $\geq$ 30, history of scarred uterus (whether CS or any uterine surgery), prior cervical procedure (cerclage,cautery),fetal macrosomia ($\geq$ 4kg),IUGR (intrauterine growth restriction), drained liquour, placenta previa, together along cases associated with co-morbidities (such as; diabetes mellitus, hypertension, cardiac disease or any maternal medical problem), or patients in need of emergency CS (antepartum hemorrhage, prolapsed pulsating cord, fetal distress) were initially excluded.

Prior to induction, fetal MCA-PI was assessed for each enrolled case using a Voluson E10 ultrasound machine. During the ultrasound (U/S) scan, other parameters as cervical length, placental site, amniotic fluid index (AFI) and estimated fetal weight (EFW) were also documented.

In measuring the fetal MCA-PI, color flow imaging was used to locate it anatomically, being detected as a major lateral branch of the circle of Willis, anterolaterally between the anterior and middle cerebral fossae. The pulsed Doppler sample gate was adjusted on the middle part of the vessel to gain the optimal flow velocity waveforms and calculate the PI (15). Hadlock's formula was used to calculate the EFW; utilizing biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), and femur length (FL) (16).

Transvaginal U/S was done for cervical length assessment. To ensure visualization of the entire cervical length, a sagittal plane of the cervix was obtained and once the view was optimal, the depth of the image was increased to occupy one thirds of the screen. Then the calipers were placed in a line between the internal and external cervical orifices (17).

The protocol for IOL followed our university hospital protocol (11). Patients were initially given 25 Mcg misoprostol vaginal tablet (Vagiprost, Adwia, Cairo, Egypt). The cervix was reassessed 6 hours after the initial dose to decide whether to repeat the dose or start oxytocin infusion (18). Patients who started the active phase of labor were transferred to the delivery room, and if necessary, augmentation of labor with oxytocin (Syntocinon, Novartis, Basel, Switzerland), and/or artificial rupture of membranes (ROM) were proceeded, under continuous electronic fetal monitoring.

Our primary outcome of concern was to document the onset of active labor, defined as 3 or more regular efficient uterine contractions (200 Montevideo units), lasting 40 seconds during 10 minutes, with a cervical dilatation more than 4 cm.

Failed induction was defined as; failure to establish active labor after a cycle of treatment of intravaginal misoprostol (25Mcg vaginal tab/6hours for 24 hours) or intravaginal misoprostol followed by oxytocin infusion after ROM up to 8 hours. Women who underwent CS before the onset of active labor for fetal (fetal distress, cord prolapse) or maternal (antepartum hemorrhage) indication were excluded.

The relation between pre-induction fetal MCA Doppler (MCA-PI) and the incidence of failure of IOL was assessed according to the collected data.

Statistical Analysis:

Sample size calculation of the current cross-sectional study was based on comparing MCA-PI between responders and non-responders in pregnant women undergoing induction of labor (IOL). Calculation was done based on comparing 2 proportions from independent samples using Chi test, the α-error level was fixed at 0.05, and the power was set at 80%. As previously published (19), the mean and SD of MCA-PI in responders (whether < 24h or > 24h) group was 1.45 ± 0.3, while it was 1.82 ± 0.3 in non-responders group. Assuming that IOL failure rate to be about 9% (19), we need to study 145 mothers to be able to reject the null hypothesis with the intended power. Accounting for dropout cases, we intended to include 150 mothers in the study. Sample size calculation was done using PS Power and Sample Size Calculations Software, version 3.1.2 for MS Windows (William D. Dupont and Walton D., Vanderbilt University, Nashville, Tennessee, USA).

Data were statistically described in terms of mean ± standard deviation (± SD), and range, or frequencies (number of cases) and percentages when appropriate. Numerical data were tested for the normal assumption using Kolmogorov Smirnov test. Comparison of numerical variables between the study groups was done using Student t test for independent samples. For comparing categorical data, Chi-square (c2) test was performed. Accuracy was represented using the terms sensitivity, and specificity. Receiver operator characteristic (ROC) analysis was used to determine the optimum cut off value for the studied diagnostic markers. Multivariate logistic regression analysis was used to test for the significant independent predictors of success of IOL. Two-sided p values less than 0.05 was considered statistically significant. IBM SPSS (Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA) release 22 for Microsoft Windows was used for all statistical analyses.

Results

A total of 150 patients were included in the study. According to the response to IOL, the cases were divided into two groups: Group 1; responders (n=133, 88.7%), in whom the onset of the active phase of labor was achieved, and, Group 2; non-responders (n=17, 11.3%), who failed to enter in the active phase of labor, as shown in figure (1).

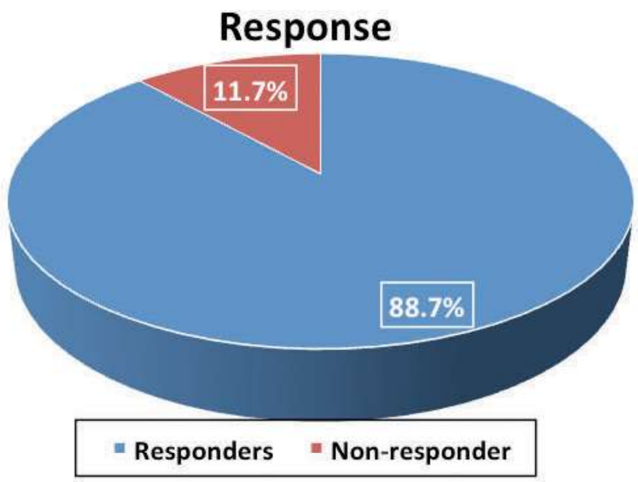

Figure (1): The distribution of response to IOL in the study sample

The baseline clinical characteristics of the enrolled cases, in either groups, as regards; maternal age, parity & BMI, are summarized in Table (1). No statistically significant difference was observed in both groups regarding the parity & BMI. However, the maternal age was significantly higher in group 1 (27.02± 4.72 years) compared to group 2 (24.06±3.45 years).

Table (1): Baseline characteristics of the studied groups.

Characteristics	Group I Responders (n=133)	Group II Non-responder (n=17)	P value
Age (in years) Mean±SD Range	 27.02±4.72 19.00-36.00	 24.06±3.45 20.00-31.00	0.014*
BMI Mean±SD Range	 24.83±2.42 20.00-29.00	 24.24±2.17 22.00-29.00	0.333
Parity P1 P2 P3 PG	 33 24.8% 38 28.6% 22 16.5% 40 30.1%	 5 29.4% 3 17.6% 1 5.9% 8 47.1%	0.353

*statistically significant

In measuring the MCA-PI prior to IOL, a statistically significant difference was noted between both groups, with lower MCAI-PI values in group 1 (1.29± 0.11) compared to group 2 (1.67±0.13)

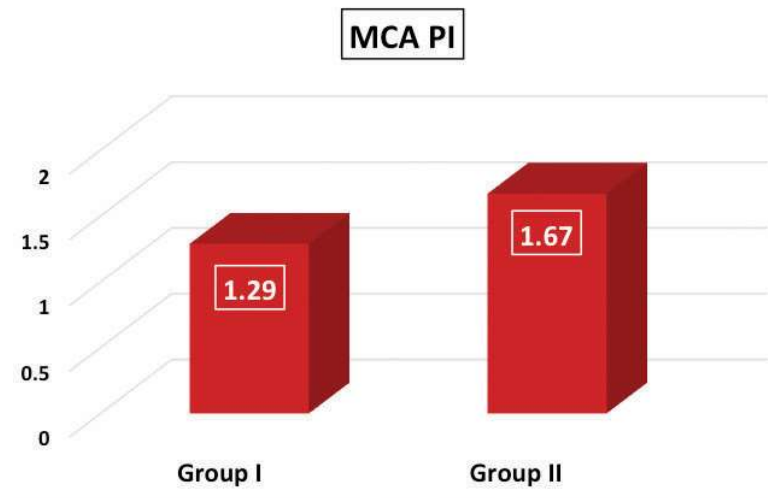

Figure (2): Fetal middle cerebral artery (MCA) pulsatility index (PI) values between the two study groups.

The other U/S parameters that were assessed prior to IOL were the cervical length (CL) and EFW. The mean of the CL was 25.28 ± 4.25 and 33.43 ± 4.80 in groups 1 and 2 respectively. The mean EFW was 3375.47 ± 178.0 and 3722.65 ± 116.33 in groups 1 and 2 respectively. There was a statistically significant difference in both variables between the two groups (P value= 0.001).

Table (2): Fetal MCA-PI values, CL, EFW between both groups.

Group	Group I Responders (n=133)	Group II Non-responder (n=17)	P
MCA-PI; Mean±s.d Range	 1.29 ± 0.11 1.07 - 1.53	 1.67 ± 0.13 1.40 - 1.92	**0.001***
Cervical length; Mean±s.d Range	 25.28 ± 4.25 16.40 - 34.10	 33.43 ± 4.80 26.40 - 41.30	**0.001***
EFW; Mean±s.d Range	 3375.47 ± 178.00 3100.0 - 3850.0	 3722.65 ± 116.33 3550.0 - 4000.0	**0.001***

*statistically significant

Receiver operating characteristics (ROC) analysis was performed to examine the ability of MCA-PI, CL and EFW in predicting the response to IOL. MCA-PI at a cutoff value 1.41 provided a sensitivity of 94.12%, and a specificity of 83.46% in predicting the outcome of IOL (in terms of the onset of the active phase of labor). The study patients were further classified according to this MCA-PI cutoff value into two groups, as shown in Table (3). In turn, the sensitivity, specificity & cutoff values of CL were 94.1%, 60.0%, 26.60, and those of EFW were 94.0%, 83.5% and 3555 respectively.

Table (3): Distribution of response according to MCA-PI cutoff value.

Characteristics		n	%
MCA PI ≤1.41	Responders	111	99.1%
	Non-responders	1	0.9%
MCA PI >1.41	Responders	22	57.9%
	Non-responders	16	42.1%

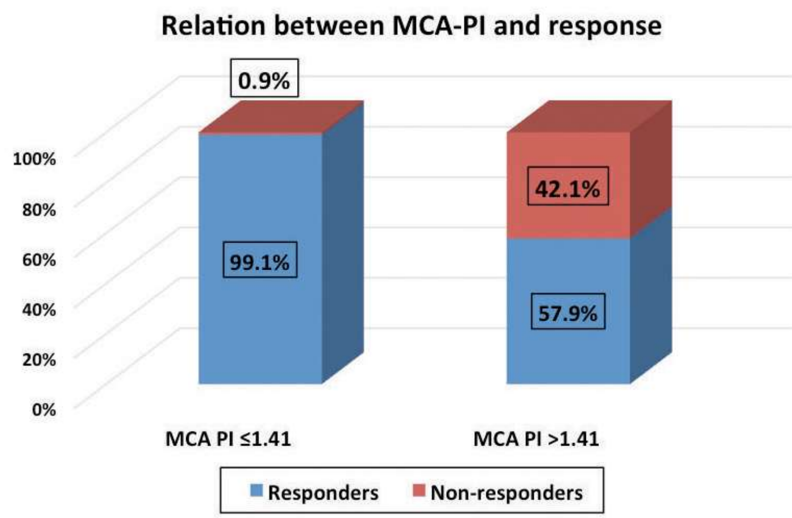

Figure (3): Distribution of response according to MCA-PI cutoff value

Variables with significant results in univariate analysis were included in multivariate logistic regression analysis. MCA PI was a significant predictor for the response even after adjustment for other variables (P=0.050).

Table (4): Multivariate logistic regression analysis for Response.

	B	SE	P value	OR	95% CI	
					LL	UL
AGE	0.545	0.482	0.258	1.724	0.671	4.430
MCA PI	25.288	12.897	0.050*	9.600	1.010	9.12
CL	0.623	0.512	0.224	1.865	0.683	5.089
EFW	0.013	0.009	0.131	1.013	0.996	1.031

B: Unstandardized Coefficients, SE: Standard Error, OR: Odds ratio, CI: Confidence interval, LL: Lower limit, UL: Upper Limit,*: Statistically significant at $p \leq 0.05$

Discussion

In current obstetric practice, postterm pregnancy necessates IOL to avoid the potential hazardous risks on the fetomaternal outcome (3, 4). Conversely, despite the extended research for the factors that may influence the process of IOL (20,21), yet, there is often great uncertainty as regards its success(19,22).

The aim of our study was to assess the value of MCA-PI for prediction of IOL outcome.

Physiologically; the onset of labor is the product of a complex mechanism, including both maternal and fetal neuroendocrinological pathways (23). As a reflection to this mechanism, the fetal Doppler parameters (especially the cerebral indices) in turn, exhibit some changes as labor approaches (13).

Based on this hypothesis, Widschwendter et al (22), further investigated the assumption that fetal Doppler indices in late pregnancy, may provide an additional criterion to predict the success and outcome of IOL. Formerly, Severi et al (13), supporting this assumption, noted that both fetal MCA-PI and resistance decrease in late pregnancy. They even nominated these indices as a signal for the onset of labor to approach.

Thus, cerebral Doppler indices are somehow correlated to the onset of labor, but the evidences available are poor (19).

Moreover, the changes that fetal MCA exhibits in early gestation should be distinguished from those that occur at term. The well known disruption in the cerebroplacental ratio (defined as RI in UA>90th centile and RI in MCA<10%), that occurs in cases of fetal growth restriction and placental insufficiency "Brain sparing", is a pathological sequence, as a reaction of fetal circulation to hostile intrauterine environment and impending fetal hypoxia. This is totally different from the so-called "term effect" of MCA indices (fall in RI and PI of MCA), which is a physiological process, that occurs late in pregnancy, secondary to vasodilatation of fetal brain vessels preceding the onset of labor (13, 14). This physiological fall in MCA resistance will allow increased oxygenation of the brain structures (24).

Another hypothesis is that this diminished resistance may trigger fetal pituitary secretion of oxytocin, which in turn stimulates labor (22). Clifton et al (25), attributed the reduction in MCA impedance together with the initiation of labor to the release of nitric oxide (NO) in placental circulation, under the effect of corticotrophin releasing hormone (CRH).

In our study, we assessed the MCA-PI in 150 patients, in late term pregnancy (41-42 weeks), who were candidates for IOL. MCA-PI was statistically significantly lower in the responder group (1.29± 0.11) compared to the non-responder group (1.67± 0.13). Additionally, MCA-PI cutoff value 1.41 achieved 94.12% sensitivity, and 83.46% specificity in prediction of IOL outcome.

Both CL and EFW were significantly lower in the responders group. This comes in agreement with several studies which supported that shorter CL, and average EFW were in favor of successful outcome for IOL (6,7,10,11,12).

Widschwendter et al (22), correlated the MCA-PI at the start of IOL with the duration. They concluded that both MCA and Bishop score may have independent effect on the duration of IOL, especially in cases beyond 41 weeks gestation. Still, their study had low statistical power, being based on a very small number of cases (n=49), and was additionally limited by the heterogeneity of their study population.

In order to achieve good accuracy in predicting the success of IOL; Vannuccini et al (19), in a prospective cohort study, proposed an ultrasound based model, including cervical length, MCA-PI, and EFW. They concluded that there is an association between MCA-PI and failed IOL, having lowest levels in those who responded within 24 hours, and highest levels in those who did not respond. They reported that a cutoff value of MCA-PI above 1.44, had 71.7% sensitivity, and 90.9% specificity as a predicting factor for failure of IOL. They included only nulliparous women, and set other factors together with MCA Doppler, instead of proving the valid correlation between MCA-PI and the onset of labor independently.

As regards our study, we preferred focusing on the MCA-PI as a sole factor, and thoroughly investigate its correlation with the onset of labor, to justify its validity and efficiency in predicting the outcome of IOL. That's why we further included all significant variables (maternal age, MCA-PI, CL, EFW) in a multivariate logistic regression analysis. MCA-PI was a statistically significant predictor for the response to IOL, even after adjustment of the other variables (P value= 0.05).

The strict selection criteria for the inclusion of our cases, together with the multivariate logistic regression analysis were aspects of strength in our work, aiming to nullify the other factors that may affect the response to IOL. Still, the sample size may be considered as a limitation, and the duration of induction was not documented in our data collection.

In conclusion; there is no doubt that vaginal delivery following IOL is the end-stay outcome of several factors, functioning in harmony together. MCA-PI evaluation prior to IOL is a useful tool in prediction of IOL outcome. Further studies on larger population are needed.

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