

Contents lists available at [ScienceDirect](https://www.sciencedirect.com)

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.journals.elsevier.com/european-journal-of-obstetrics-and-gynecology-and-reproductive-biology

Full length article

Prediction of intrapartum fetal compromise at the end of pregnancy; is Doppler, and not weight, that matters

José Morales-Roselló^{a,b,*}, Asma Khalil^{c,d}^a Servicio de Obstetricia y Ginecología, Hospital Universitario y Politécnico La Fe, Valencia, Spain^b Departamento de Pediatría, Obstetricia y Ginecología, Facultad de Medicina y Odontología, Universidad de Valencia, Spain^c Fetal Medicine Unit, St George's Hospital, London, UK^d St George's University of London, London, UK

ARTICLE INFO

Keywords:

Cerebroplacental ratio
Fetal growth
Middle cerebral artery Doppler
Labor outcome
Intrapartum compromise
Cardiotocogram
Fetal monitoring

ABSTRACT

Despite the fact that labor depends on too many interacting factors and no parameter can fully predict its outcome, fetal cerebral Doppler has emerged as the most reliable tool for prediction, in contrast with fetal weight, which performs significantly worse in the last weeks of pregnancy. The importance of the cerebral Doppler follows the inverse pathway of fetal weight increasing its performance in the last weeks of pregnancy and reaching its highest ability prior to labor. A combination of cerebral flow, fetal weight, and selected clinical information may obtain moderate predictions of labor outcome, provided the interval to labor is not long.

Introduction; the drawbacks of fetal weight

Fetal wellbeing surveillance at term, aims to rule out late-onset nutritional dysfunction as it exerts a subtle but important influence on fetal neurogenesis [1]. Ultrasound is the gold standard for its detection. However, until recently, it was simply used as a biometric instrument with the aim of detecting fetal growth below the 10th centile in the belief that fetal smallness included most nutritional disorders. However, during the last weeks of pregnancy, the association of fetal size with normal nutrition has been found to be poor for several reasons. On the one hand, half of fetuses growing below the 10th centile and classified as small for gestational age (SGA) are simply genetically small, and on the other, some of the fetuses growing over the 10th centile and classified as appropriate for gestational age (AGA) present abnormal nutrition and are at risk of intrapartum fetal compromise (IFC) or even stillbirth. Moreover, there is still no consensus regarding which are the best fetal references, thus making the choice of the 10th centile an arbitrary decision that also influences the sensitivity and specificity of ultrasound for the prediction of IFC. Finally, the efficacy of fetal biometry for the prediction of IFC is inversely proportional to gestational age (GA) and decreases significantly after week 34. A clear example of this is stillbirth, which at this period occurs more frequently in appropriate for gestational age fetuses (AGA), while in earlier weeks it is more frequent in

fetuses that are small [2–5].

The proposal of a new hemodynamic model

These diagnostic shortcomings prompted us to propose another diagnostic model based on fetal hemodynamics using the middle cerebral artery Doppler and its ratio to the umbilical Doppler, the cerebroplacental ratio (CPR). A model that focused on those fetuses with normal weight and abnormal CPR that were not considered at risk in the classical weight model [6,7] (Fig. 1). In summary, the hemodynamic model takes advantage of the physiological cerebral vasodilation and the consequent decrease in impedance that occurs during late-onset growth restriction, regardless of fetal weight, and therefore is able to explain why some AGA fetuses at the end of pregnancy end up with adverse outcomes or even die.

The hemodynamic versus the weight model

Considering both models, we might wonder which one provides more information for the prediction of intrapartum compromise. To elucidate this question, several strategies may be undertaken. The first is to compare the risk among groups using a simple scheme. If we plot CPR in multiples of the median (MoM) against estimated fetal weight (EFW)

* Corresponding author at: Servicio de Obstetricia y Ginecología, Hospital Universitario y Politécnico La Fe, Valencia, Spain.

E-mail address: jose.morales@uv.es (J. Morales-Roselló).

<https://doi.org/10.1016/j.ejogrb.2024.07.070>

Received 26 April 2024; Accepted 31 July 2024

Available online 5 August 2024

0301-2115/© 2024 The Author(s). Published by Elsevier B.V. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

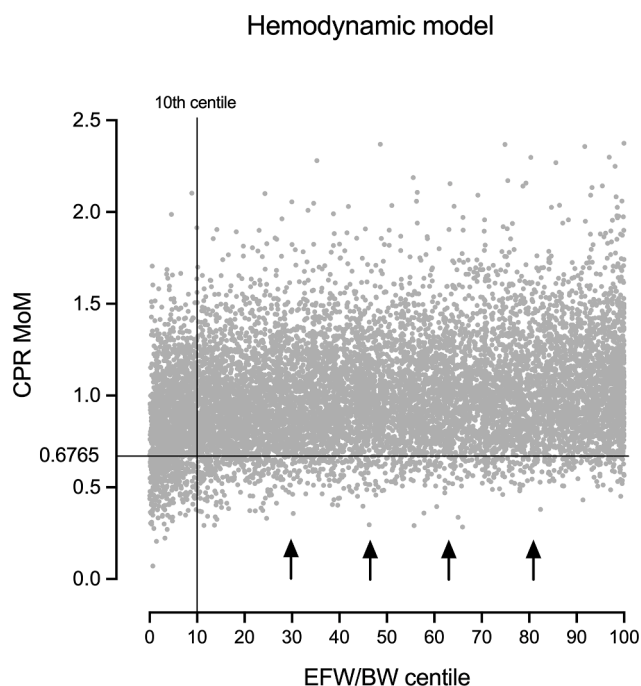


Fig. 1. Hemodynamic model plot. Arrows indicate fetuses with normal EFW and abnormal CPR MoM.

in centiles (Fig. 1), we will be able to represent all cases with different GA. In this scheme, two perpendicular lines crossing the EFW 10th centile and the CPR 0.6765 MoM (a figure equivalent to the 5 % percentile) define four groups, with the most interesting being that in which only the EFW centile is abnormal and that in which only the CPR MoM is abnormal (Fig. 1, arrows). In several works, we compared the risk of IFC or adverse perinatal outcome (APO) in both groups, observing that it was worse to present an abnormal CPR MoM than to present an abnormal EFW, thus indicating that hemodynamics was a more important determinant than weight for the prediction of IFC [8–10].

We may also approach this comparison by means of logistic regression. Univariable logistic regression, allows us to compare every determinant's efficacy by means of its area under the curve (AUC), odds ratio (OR), and P-value. In one study, we compared the three different ways to calculate the EFW centile (population, Intergrowth-21st, and customized references) with the CPR MoM for the prediction of IFC. Our results indicated that the efficacy of CPR MoM surpassed that of the EFW centile, whatever the methods applied to calculate it [11].

The problem with univariable regression is that it does not adjust for confounding determinants. However, it is possible to perform multivariable regression that adjusts for different plausible parameters, comparing all the determinants in unison by means of their AUC, OR, and P-value. We have performed several studies in which both determinants, the EFW centile and the CPR MoM, were included and studied in the last weeks of pregnancy. In one of them, we collected cases in which stillbirth occurred within two weeks of examination to evaluate determinants associated with stillbirth. Although the prediction model was poor, it showed that the only significant determinant in the prediction of stillbirth was CPR MoM and not EFW centile [12]. In another work, we evaluated plausible determinants for the prediction of APO and IFC one day before labor. The multivariable model showed that the only significant parameters were the CPR MoM and the type of labor onset (induction), but not the EFW centile [13]. Interestingly, the prediction ability was notable, with an AUC close to 0.80, and did not differ much from the ability obtained by CPR MoM alone, proving that the interval examination-labor was crucial for the prediction of labor outcomes. A third study investigated the determinants of APO over 34

weeks, but within two weeks of labor. As expected, due to the longer interval, the AUC was lower. However, the only significant determinants were the CPR MoM, the type of labor onset (induction), and the parity, but again not the EFW centile [14]. A fourth study investigated the importance of determinants in the prediction of APO, but in this case before 34 weeks. Only the EFW centile, CPR MoM, and GA, but not the uterine Doppler or the type of labor onset, were significant, proving that even in the early third trimester, when the importance of EFW is notorious, CPR MoM keeps on being as important as the EFW centile in the prediction of APO [15]. Finally, not only our group but also other researchers have concluded that the importance of hemodynamics surpasses that of EFW. In two works performed by Triunfo et al [16], and Rizzo et al [17], the authors concluded that CPR MoM was more important than the EFW centile, which in both cases turned out to be not significant for the prediction of APO in the last weeks of pregnancy.

An extension of the multivariable analysis is the contour and 3D graph representation. The possibility of APO may be plotted as a 3D graph, surface planes, or contour graphs in which the chosen APO (for example, the neonatal pH) is represented according to the values of the CPR MoM or growth centile, forming a graph that resembles a tilted surface plane, an isoline (contour) graph, or even a 3D representation. Using this methodology, our results showed how the pH isolines changed more intensely using the CPR axis, how the pH plane was tilted in the direction of pH, or how the depth of the 3D figure was higher where CPR values were lower, proving again that CPR MoM was more important than fetal weight in the explanation of the neonatal pH [18].

Expectancies with the hemodynamic approach

All the above-mentioned studies indicate that in the last weeks of pregnancy, CPR MoM is more important than fetal weight for the prediction of APO and IFC and underline its crucial importance as a tool to evaluate fetal wellbeing. Of note, this assertion has been recently validated by a clinical trial proving the importance of CPR in the reduction of perinatal morbidity [19].

Despite CPR being the best known determinant for IFC/APO, its prediction ability remains poor. However, its prediction ability might be increased with the addition of other clinical parameters. Unfortunately, so far, the results of the prediction models published by other groups have been poor, with AUC values close to 0.60. And although those published by us perform slightly better, their ability to predict APO/IFC still remains within the moderate range, probably because all the prediction determinants, especially those related to fetal hemodynamics, are strongly dependent on the proximity to the actual date of labor [20].

Conclusion

We might conclude by saying that fetal surveillance at the end of pregnancy should be approached by means of Doppler ultrasound and CPR, although fetal biometry with EFW calculation, and other clinical parameters should also be considered.

CRediT authorship contribution statement

José Morales-Roselló: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Asma Khalil:** Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

- [1] Eixarch E, Muñoz-Moreno E, Bargallo N, Bataille D, Gratacos E. Motor and corticostriatal-thalamic connectivity alterations in intrauterine growth restriction. *Am J Obstet Gynecol* 2016;214(725):e1–9.
- [2] Poon LC, Tan MY, Yerlikaya G, Syngelaki A, Nicolaides KH. Birth weight in live births and stillbirths. *Ultrasound Obstet Gynecol* 2016;48:602–6.
- [3] Bakalis S, Akolekar R, Gallo DM, Poon LC, Nicolaides KH. Umbilical and fetal middle cerebral artery Doppler at 30–34 weeks' gestation in the prediction of adverse perinatal outcome. *Ultrasound Obstet Gynecol* 2015;45:409–20.
- [4] Thilaganathan B. Ultrasound fetal weight estimation at term may do more harm than good. *Ultrasound Obstet Gynecol* 2018;52:5–8.
- [5] Willinger M, Ko CW, Reddy UM. Racial disparities in stillbirth risk across gestation in the United States. *Am J Obstet Gynecol* 2009;201(469):e1–8.
- [6] Morales-Roselló J, Khalil A. Fetal cerebral redistribution: a marker of compromise regardless of fetal size. *Ultrasound Obstet Gynecol* 2015;46:385–8.
- [7] Morales-Roselló J, Khalil A, Morlando M, Bhide A, Papageorghiou A, Thilaganathan B. Poor neonatal acid-base status in term fetuses with low cerebroplacental ratio. *Ultrasound Obstet Gynecol* 2015;45:156–61.
- [8] Morales-Roselló J, Khalil A, Martínez-Varea A. Management of fetuses with apparent normal growth and abnormal cerebroplacental ratio: a risk-based approach near term. *Acta Obstet Gynecol Scand* 2024;103:334–41.
- [9] Khalil AA, Morales-Rosello J, Morlando M, Hannan H, Bhide A, Papageorghiou A, Thilaganathan B. Is fetal cerebroplacental ratio an independent predictor of intrapartum fetal compromise and neonatal unit admission? *Am J Obstet Gynecol* 2015;213:54.e1–54.e10.
- [10] Khalil AA, Morales-Rosello J, Elsaddig M, Khan N, Papageorghiou A, Bhide A, Thilaganathan B. The association between fetal Doppler and admission to neonatal unit at term. *Am J Obstet Gynecol* 2015;213:57.e1–7.
- [11] Morales-Roselló J, Cañada Martínez AJ, Scarinci E, Perales Marín A. Comparison of cerebroplacental ratio, intergrowth-21st standards, customized growth, and local population references for the prediction of fetal compromise: which is the best approach? *Fetal Diagn Ther* 2019;46:341–52.
- [12] Morales-Roselló J, Galindo A, Herraiz I, Gil MM, Brik M, De Paco-Matallana C, Ciannella R, Sanchez Ajenjo C, Cañada Martínez AJ, Delgado JL, Perales-Marín A, Spanish Group for the Study of Stillbirth. Is it possible to predict late antepartum stillbirth by means of cerebroplacental ratio and maternal characteristics? *J Matern Fetal Neonatal Med* 2020;33:2996–3002.
- [13] Morales-Roselló J, Loscalzo G, Jakaitė V, Perales Marín A. The diagnostic ability of the cerebroplacental ratio for the prediction of adverse perinatal outcome and intrapartum fetal compromise within one day of delivery. *Gynecol Obstet Invest* 2021;86:343–52.
- [14] Morales-Roselló J, Loscalzo G, Jakaitė V, Buongiorno S, Perales Marín A. Healthy mothers with normal cardiotocograms at term. Is maternal age a true determinant of perinatal outcome? *J Matern Fetal Neonatal Med* 2022;35:9843–50.
- [15] Morales-Roselló J, Galindo A, Scarinci E, Herraiz I, Buongiorno S, Loscalzo G, Gómez Arriaga PI, Cañada Martínez AJ, Rosati P, Lanzone A, Perales Marín A. Predictors of adverse perinatal outcome up to 34 weeks, a multivariable analysis study. *J Obstet Gynaecol* 2022;42:1058–64.
- [16] Triunfo S, Crispi F, Gratacos E, Figueras F. Prediction of delivery of small-for-gestational-age neonates and adverse perinatal outcome by fetoplacental Doppler at 37 weeks' gestation. *Ultrasound Obstet Gynecol* 2017;49:364–71.
- [17] Rizzo G, Mappa I, Bitsadze V, Słodki M, Khizroeva J, Makatsariya A, D'Antonio F. Role of Doppler ultrasound at time of diagnosis of late-onset fetal growth restriction in predicting adverse perinatal outcome: prospective cohort study. *Ultrasound Obstet Gynecol* 2020;55:793–8.
- [18] Morales-Roselló J, Khalil A, Alberola-Rubio J, Hervas-Marín D, Morlando M, Bhide A, Papageorghiou A, Perales-Marín A, Thilaganathan B. Neonatal acid-base status in term fetuses: mathematical models investigating cerebroplacental ratio and birth weight. *Fetal Diagn Ther* 2015;38:55–60.
- [19] Rial-Crestelo M, Lubusky M, Parra-Cordero M, Krofta L, Kajdy A, Zohav E, Ferriols-Perez E, Cruz-Martinez R, Kacerovsky M, Scazzocchio E, Roubalova L, Socias P, Haslík L, Modzelewski J, Ashwal E, Castellá-Cesari J, Cruz-Lemini M, Gratacos E, Figueras F, RATIO37 Study Group. Term planned delivery based on fetal growth assessment with or without the cerebroplacental ratio in low-risk pregnancies (RATIO37): an international, multicentre, open-label, randomised controlled trial. *Lancet* 2024;403:545–53.
- [20] Morales-Roselló J, Khalil A, Loscalzo G, Buongiorno S, Brik M, Mendoza M, Di Fabrizio C, Scarinci E, Salvi S, Lanzone A, Perales Marín A. Cerebroplacental ratio prediction of intrapartum fetal compromise according to the interval to delivery. *Fetal Diagn Ther* 2022;49:196–205.