MODELLING BIRTHWEIGHT AS A FUNCTION OF GESTATIONAL AGE AT DELIVERY IN HYPERTENSIVE DISORDER OF PREGNANCY

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Introduction

Pre-eclampsia (PE) is a multifactorial syndrome with different clinical phenotypes. To address this heterogeneity, the syndrome has been subdivided, according to gestational age (GA), into early and late PE, but this classification is not completely satisfying [1]. The most-studied clinical phenotype is that caused by shallow trophoblastic invasion of the spiral arteries, with oxidative stress and release of placental factors, which lead to endothelial dysfunction and organ damage [2]. Doppler velocimetry of the uterine arteries (UtA-PI) and measurement of vascular growth factors can be used to screen for early vascular damage, associated with reduced placental growth and intrauterine growth restriction (IUGR) later in pregnancy [3]. This clinical phenotype is predominant in cases prior to 34 wks of GA, thus early PE can be regarded as a proxy for cases affected by this sequence of events. Anyhow, the disease does not end at 34 wks of GA, and less severe cases represent a large proportion of syndromic manifestations of PE in late gestation [1]. Cases affected by hypertensive disorders of pregnancy (HDP) including PE are frequently found to have normal neonates and placentas [4]. In these cases, endothelial dysfunction can be ascribed to the placental pro-inflammatory response, dyslipidemia or other pro-inflammatory conditions resulting in low-grade inflammation due to pre-existing maternal conditions, such as maternal metabolic syndrome and cardiovascular risk factors. These risk factors are not suppposed to operate only from 34 wks of GA onwards.

The aim of this presentation is to verify whether a classification based only on fetal abdomen circumference (AC) and UtA-PI is suitable for defining two internally homogeneous subgroups of women affected by HDP, characterized by different effects on fetal growth, as can be inferred from the outcome, in terms of birthweight conditional on GA, and whether GA at the onset of HDP has a role in determining fetal growth.

Data and methods

This multicentre study includes all eligible cases of HDP consecutively admitted over a 12-month period (from December 2013) to seven Italian tertiary referral centres for maternal-fetal medicine. To be eligible for inclusion, the clinical records of each patient had to report two "key items": fetal assessment of abdomen circumference (AC) and mean UtA-PI. Women with multiple pregnancy and with chromosomal or structural fetal abnormalities were excluded. A total of 902 patients met these inclusion/exclusion criteria. Data concerning maternal characteristics, pregnancy complications and outcome were retrieved from the archived clinical records [5].

Pregnant women were grouped into two phenotypes, independently of GA at the onset of HDP. The first phenotype, which was named HDP-IUGR (n=124) [5], is characterized by maternal HDP associated with fetal AC at admission below the 5th centile of Todros *et al* reference [6], and an abnormal UtA-PI, defined as mean of right and left UtA-PI>95th centile of Gomez *et al* reference [7]. The second phenotype, which was named HDP-AGA, i.e. fetuses whose AC is appropriate-for-gestational age (n=205), is characterized

by maternal HDP associated with fetal AC≥5th centile and UtA-PI≤95th centile. The group was then subdivided in early and late-onset HDP, depending whether GA at the onset of disease was <34+0 or ≥34+0 wks+days. The remaining patients were excluded because of missing data on either fetal AC or UtA Doppler velocimetry (n=461), or because discordant values of fetal AC and UtA Doppler velocimetry (n=112), i.e. AC at admission ≥5th centile and UtA-PI>95th centile, or AC at admission <5th centile and UtA-PI≤95th centile.

To model birthweight as a function of GA at delivery we resorted to the generalization of the logistic function introduced by von Bertalanffy [8], which can be written as [9]:

$$E(y(t)) = \frac{\kappa}{\left(1+\alpha e^{-\beta(t-\tau)}\right)^{1/\alpha}}$$

where E(y(t)) is the value of the birthweight y expected at GA t on the basis of the model, κ is the upper asymptote (ideally birthweight at term), β is a velocity constant and τ is GA at the inflection point, i.e. the age at which maximum growth velocity occurs, α determines the degree of asymmetry of the function. On this function was based the model used to trace the INeS (Italian Neonatal Study) reference charts [10].

The effect of sex (x_1), phenotype (x_2) and gestational age at admission (x_3) were modelled introducing the proper multiplicative terms into the nonlinear model:

$$E(y(t)) = \frac{\kappa(1+\vartheta x_1)(1+\xi x_2)(1+\varphi x_3)}{\left(1+\alpha e^{-\beta(t-\tau)}\right)^{1/\alpha}}$$

where x_1, x_2, x_3, are 1 when sex is male, clinical phenotype is HDP-IUGR, GA at the onset of HDP is <34+0 wks+days, respectively, and is 0 otherwise; parameters ϑ, ξ and ϕ are the proportional increase in birthweight due to the effect of these conditions. Least-squares estimates of the parameters of the above model were obtained with Marquardt algorithm, resorting to SAS PROC NLIN of SAS/STAT® software (SAS Institute, Cary, NC; v.9.4, 2013).

Results

Figure 1 shows birthweight as a function of GA at delivery in neonates classified by sex, maternal phenotype and GA at the onset of HDP. When the model includes only the term accounting for the effect of sex, birthweight of males is estimated to be higher than that of females by 4% (95%CL: 1%, 7%; p=0.0158). The introduction of the term expressing the effect of phenotype into the model consistently improves the goodness of fit: the coefficient of determination increased from 0.86 to 0.91 and the residual standard deviation decreased from 366 to 294 g. The children of women with phenotype HDP-IUGR show a birthweight lower by 23% (95%CL: 20%, 26%; p<0.0001) than those of women with phenotype HDP-AGA. No further improvement in model fit was observed when GA at admission was added to the model. This result was confirmed when birthweight was expressed as standard deviation score (SDS), on the basis of the INeS reference charts [10], so as to remove the effect of gestational age at delivery, birth order and sex. The mean birthweight SDS (±standard error) of babies delivered by HDP-IUGR women was -1.53±0.05 (corresponding to the 6th centile) *vs* -0.05±0.06 (corresponding to the 48th centile) for babies delivered by HDP-AGA women (p<0.0001). As emerges from figure 1, GA at the onset of HDP did not appear to exert any effect on birthweight. At each GA, the children born to women with late onset of HDP (≥34 wks) show birth weights close to those of children born to women with early onset of HDP (<34 wks), the difference being about 1% (95%CL: -2%, 4%; p=0.5116).

Conclusions

The use of the parametric nonlinear model presented in this study yielded a synthetic and faithful description of the relationship between birthweight and GA in over 3 hundred babies born to women

suffering with hypertensive disorders of pregnancy, and delivered between the 25th and the 42nd week of GA. Furthermore the model provided estimates of the separate effects that sex, HDP phenotype, and GA at the onset of HDP exert on birthweight.

Among babies born to HDP mothers, birthweight of males was found to be higher than that of by 4%: an identical difference was observed in the reference set used to trace INeS charts [10], this suggest that HDP impairs fetal growth independently of sex. The babies born to mothers with phenotype HDP-IUGR were found to have birthweight lower by about 25% than those born to mothers with phenotype HDP-AGA: this is not unexpected, fetal weight being partly determined by abdomen volume. Nonetheless, since delivery occurred, on the average, 3 weeks after the assessment of abdomen circumference, such a difference suggests the persistence of conditions unfavourable to fetal growth up to end of pregnancy. The third hypothesis that the model could test was whether GA at the onset of HDP affects the severity of fetal growth impairment. In this case we would expect that birthweight of babies born to mothers with early onset of HDP is considerably lower. Results showed that fetal growth follows the same pattern, independently of GA at the onset of HDP.

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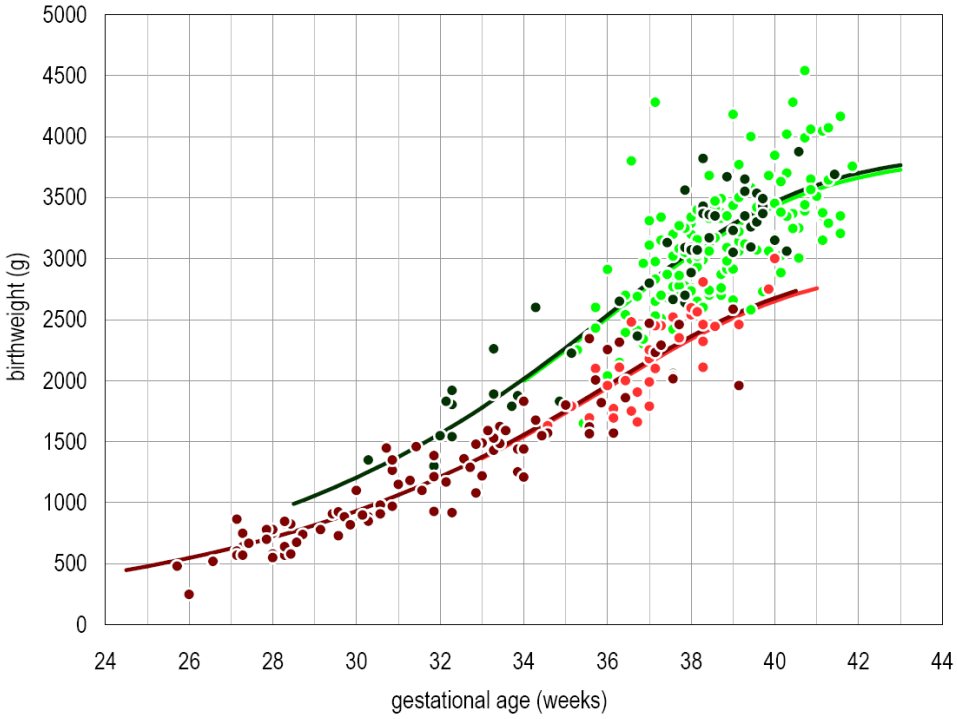

Figure 1. Birthweight as a function of GA at delivery in cases of hypertensive disorder of pregnancy (HDP) with intrauterine growth restriction (IUGR) or appropriate-for-gestational age (AGA) fetuses, with early (<34 wks) or late (≥34 wks) GA at the onset of HDP. Individual data points on fitted curve are plotted for each subgroup: dark green, HDP-AGA<34 wks (n=52); light green, HDP-AGA≥34 wks (n=153); dark red, HDP-IUGR<34 wks (n=87); light red, HDP-IUGR≥34 wks (n=37). Continuous curves were traced using a nonlinear model based upon the generalized logistic function [8], and are adjusted for the effect of sex.

TEMA DELLA COMUNICAZIONE:
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