Placenta 42 (2016) 93–105

Contents lists available at ScienceDirect

Placenta

journal homepage: www.elsevier.com/locate/placenta

Clustering and classical analysis of clinical and placental phenotypes in fetal growth restriction and constitutional fetal smallness☆

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ARTICLE INFO

Article history:
Received 26 August 2015
Received in revised form
4 April 2016
Accepted 9 April 2016

Keywords:
Fetal growth restriction
Placenta
Small-for gestational age
Early-onset
Late-onset

ABSTRACT

This study aims to determine whether placental examination can be used to distinguish between pathologic fetal growth restriction (FGR) and constitutional fetal smallness. Data were extracted from a clinicoplacental database of high risk pregnancies during the period 1994–2013. These data were used to compare the 590 consecutive cases having birth weights below the 10th percentile with the 5201 remaining cases having gestational ages ≥20 weeks. The authors analyzed 20 clinical and 46 placental phenotypes using classical statistics, clustering analysis, and multidimensional scaling. Of the low-birth-weight babies, the following types of cases were compared:

- 246 cases with the clinical risk factors most discriminative for FGR were compared with 344 cases without these risk factors (gestational hypertension or severe preeclampsia, maternal substance abuse and/or smoking, oligohydramnios, and abnormal umbilical artery Dopplers), and
- 196 early-onset cases were compared with 394 late-onset cases.

Four categories of placental phenotypes (those with features of poor uteroplacental perfusion, post-uterine placental pathology, chronic inflammation, and a mixed category) better defined the presumably true FGR than did the clinical phenotypes. Maternal smoking and oligohydramnios were associated with fewer abnormal placental phenotypes than were maternal hypertensive diseases and abnormal Dopplers. Early-onset cases of fetal smallness clustered with placental features of poor uteroplacental perfusion, whereas late onset cases did not. Placental examination helps to retrospectively distinguish constitutionally small fetuses from those that are pathologically growth restricted. The latter correlate best with the clinical risk for FGR and with early-onset FGR. This correlation may have prognostic significance for the child and for future pregnancies, since hypoxic placental lesions can occur without clinical risk factors but with a tendency to recur in future pregnancies.

1. Introduction

Fetal growth restriction (FGR) is the failure of a fetus to achieve its growth potential at a given gestational age. This condition affects 7%–15% of all pregnancies and may be associated with adverse pregnancy outcomes [1], particularly with a 5- to 10-fold increase in risk of stillbirth [2]. The etiologies of FGR include maternal, fetal, and placental factors [3–6]. The latter are especially numerous [2–6]. Clinically, two subtypes of FGR have been distinguished: early-onset and late-onset. Early-onset FGR is commonly characterized by absent or reversed end-diastolic flow velocity in the umbilical arteries [7].

FGR is regarded as a late manifestation of early dysfunction during placental development [8].

Various placental abnormalities have been associated with FGR [6,9], particularly with asymmetric FGR [10]. The most commonly

☆ Presented at the International Federation of Placenta Associations meeting, Paris, France, September 9–12, 2014.

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http://dx.doi.org/10.1016/j.placenta.2016.04.012
0143-4004/

Table 1
Small birth weight in high risk pregnancy.

	Pregnancy complications and outcomes without fetal growth restriction	Pregnancy complications and outcomes with fetal growth restriction	Prevalence of fetal growth restriction in pregnancy complications, outcomes and placental abnormalities (%)	Yates chi-square/F between columns 2 and 3	P Bonferroni
Number of cases	5201	590			
A. Clinical phenotypes					
Gestational age (weeks, average ± standard deviation)	33 ± 6	33 ± 6		1.1	
Substance abuse and/or maternal smoking	281 (5)	61 (10)	18	22.3	<0.001
Gestational hypertension	59 (1)	23 (4)	28	27.0	<0.001
Preeclampsia					
Mild	157 (3)	32 (5)	17	9.0	
Severe, including superimposed	161 (3)	46 (8)	22	32.6	<0.001
HELLP (Hemolysis, Elevated Liver enzymes, Low Platelets)	54 (1)	14 (2)	21	7.0	
Chronic hypertension (excluding superimposed preeclampsia)	98 (2)	18 (3)	15	3.1	
Maternal diabetes mellitus (excluding superimposed preeclampsia)	291 (6)	20 (3)	6	4.6	
Oligohydramnios	244 (5)	115 (19)	32	197.1	<0.001
Premature rupture of membranes	758 (15)	40 (7)	5	26.4	<0.001
Antepartum hemorrhage	606 (12)	28 (5)	4	27.2	<0.001
Abnormal fetal heart rate tracing[a]	792 (15)	119 (20)	13	9.4	
Abnormal umbilical artery Dopplers	36 (1)	62 (10)	63	301.0	<0.001
Induction of labor	348 (7)	119 (20)	25	128.0	<0.001
Cesarean section	1842 (35)	232 (39)	11	3.3	
Neonatal mortality	220 (4)	16 (3)	7	2.7	
Nonmacerated stillbirth	240 (4.6)	17 (2.9)	6.6	3.4	
Macerated stillbirth	341 (6)	78 (13)	19	34.1	<0.001
Multiple pregnancy	553 (11)	41 (7)	7	7.4	
B. Placental phenotypes					
Placental weight (grams, average ± standard deviation)	394 ± 189	296 ± 151		143.4	
Inflammation					
Acute chorioamnionitis					
Maternal inflammatory response	1396 (27)	108 (18)	7	19.6	<0.001
Fetal inflammatory response	626 (12)	34 (6)	5	20.0	<0.001
Villitis of unknown etiology	423 (8)	77 (13)	15	15.6	0.006
Plasma cell deciduitis	115 (2)	28 (8)	20	13.1	0.022
Hypoxia-related lesions					
Fetal					
Erythroblastosis of fetal blood	286 (5)	46 (8)	14	4.8	
Maternal					
Villous infarction (>5% of placental parenchyma)	492 (9)	120 (20)	20	65.2	<0.001
Hypertrophic decidual arteriolopathy	750 (14)	149 (25)	17	46.6	<0.001
Atherosis of spiral arterioles	174 (3)	60 (10)	26	61.9	<0.001
Laminar necrosis of membranes[b]	693 (13)	130 (22)	16	32.3	<0.001
Patterns of diffuse hypoxic injury					
Preuterine	293 (6)	31 (5)	10	0.1	
Uterine	218 (4)	73 (12)	25	72.6	<0.001
Postuterine	120 (2)	56 (9)	32	90.4	<0.001
Membrane chorionic microcysts[c]	347 (7)	58 (10)	14	7.6	
Chorionic disc chorionic microcysts[d]	215 (4)	55 (9)	20	30.9	<0.001
Maternal floor multinucleate trophoblastic giant cells	392 (7)	97 (16)	20	53.2	<0.001
Excessive amount of extravillous trophoblasts in chorionic disc	227 (4)	71 (12)	24	62.3	<0.001