International Journal of Gynecology and Obstetrics 120 (2013) 165–168

Contents lists available at SciVerse ScienceDirect

International Journal of Gynecology and Obstetrics

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

CLINICAL ARTICLE

A case–control study of placental lesions associated with pre-eclampsia

Louise Devisme [a], Benjamin Merlot [b,*], Anne Ego [b], Veronique Houfflin-Debarge [b], Philippe Deruelle [b], Damien Subtil [b,c]

[a] Department of Pathology, Biology-Pathology Center CHRU de Lille, Lille Cedex, France
[b] Jeanne de Flandre Hospital, Lille Nord de France University, Lille, France
[c] EA 2694, Lille Nord de France University, Lille Cedex, France

ARTICLE INFO

Article history:
Received 14 November 2011
Received in revised form 3 August 2012
Accepted 25 October 2012

Keywords:
Hypoxia
Ischemia
Placental lesion
Pre-eclampsia
Pregnancy

ABSTRACT

Objective: To investigate gross and microscopic placental lesions associated with pre-eclampsia and to determine which lesions are most strongly linked to serious pregnancy complications. *Methods:* A retrospective case–control study of 173 placentas from women with pre-eclampsia and 173 placentas from healthy normotensive women was conducted. *Results:* The mean placental weight in the pre-eclampsia group was lower than that recorded for the control group (280 g vs 360 g; $P<0.001$). Infarcts (65.9% vs 13.2%; $P<0.001$) and placental abruption ($P<0.001$) were most frequent among women with pre-eclampsia. Microscopic findings showed the following lesions to be associated with pre-eclampsia: hypermature villi, defined by absence of intermediate villi (72% vs 16%; $P<0.001$), excessive syncytial knots (90% vs 9%; $P<0.001$), decidual vasculopathy (51% vs 8%; $P<0.001$), villous fibrosis (6% vs 0%; $P<0.001$), erythroblastosis (11% vs 4%; $P<0.01$), and avascular terminal villi (9% vs 3%; $P<0.05$). Increased syncytial knots, infarcts, basal decidual vasculopathy, hypermature villi, and placental erythroblastosis were still associated with pre-eclampsia after logistic regression modeling. *Conclusion:* Placental lesions most strongly associated with pre-eclampsia were all causes or expressions of placental hypoxia or ischemia, which appears as the primary mechanism of pre-eclampsia.

1. Introduction

Pre-eclampsia is defined as the association of pregnancy-related hypertension and proteinuria exceeding 300 mg every 24 hours [1]. In its most severe form, pre-eclampsia affects approximately 2% of all pregnancies and threatens the health of both mother and fetus. Estimates suggest that 50 000 women die worldwide from this disease every year and that it is one of the leading causes of induced preterm delivery [2].

Pre-eclampsia may result from different causes, all of which lead to placental insufficiency, either absolute or relative, which in turn is the source of maternal and fetal complications. Possible causes of pre-eclampsia might include immunologic conflict between mother and fetus, defective trophoblastic invasion of the arteries, excess fetal and placental volume to be perfused (molar or multiple pregnancies), and placental thrombosis owing to genetic thrombophilia [3]. Regardless of the cause or etiologic hypothesis, the placenta seems to have a fundamental role in the development of pre-eclampsia, and only its delivery permits complete regression of symptoms.

No placental lesion is pathognomonic of pre-eclampsia [4]; however, those described in the literature generally suggest an ischemic, thrombotic, or inflammatory cause [5]. As such lesions are numerous and frequently inter-related, it is difficult to study the respective roles of these different pathophysiologic mechanisms in the onset of pre-eclampsia. The aim of the present study was, therefore, to define the gross and microscopic placental lesions associated with pre-eclampsia and to determine which lesions are most strongly linked to serious pregnancy complications.

2. Materials and methods

A retrospective case–control study was conducted that reviewed the records of placental examinations performed in the pathology department of our regional university hospital in Lille, France. Placentas from consecutive pre-eclamptic pregnancies (n = 173) that presented between February 2005 and April 2008 were selected according to the clinical data but independent of the pathology report. The diagnosis of pre-eclampsia required systolic blood pressure at or above 140 mm Hg and diastolic pressure at or above 90 mm Hg, with proteinuria equal to or greater than 300 mg/L. A control group of 173 placentas—which were obtained during the same time period from pregnant women with no mention in their records of vascular problems—was also created. The controls were matched to the pre-eclampsia cases according to gestational age, most often to within 1 day. Control placentas derived from pregnancy terminations for fetal malformations (n = 73; 42.2%), spontaneous premature deliveries (n = 61; 35.3%), and cesarean deliveries performed owing to uterine malformation or

* Corresponding author at: Department of Obstetrics, Jeanne de Flandre Hospital, Université Lille II, 1 rue Eugène Avinée, 59037 Lille Cedex, France. Tel.: +33 3 20 44 66 26; fax: +33 3 20 44 63 11.
E-mail address: benmerlot@gmail.com (B. Merlot).

0020-7292/$ – see front matter
http://dx.doi.org/10.1016/j.ijgo.2012.08.023

abnormal placental insertion (n = 39; 22.5%). Because the present study was retrospective, patient consent was not required.

All of the placentas were examined according to previously published guidelines [6–8]. Placentas were weighed, fixed in a 10% solution of neutral formalin, and assessed for gross abnormalities. The placental weight was related to the mean reference weight for gestational age [9], calculating the percentage decrease or increase of the actual-to-theoretical placental weight for gestational age. Apparent "old" and "recent" infarcts were counted and the area affected estimated as a percentage of the total area of the placenta. Retroplacental hematomas, which compressed the basal plate, were distinguished from marginal hematomas located near the zone of membrane insertion. Subchorionic thrombosis, located at the ceiling of the intervillous space, was distinguished from intervillous thrombosis within the intervillous space. Finally, cord anomalies—single umbilical artery or velamentous insertion—as well as the presence of placental chorangioma were systematically recorded [5–7,9].

At least 3 tissue samples were routinely taken for microscopic examination, comprising 2 full-thickness samples from the placental parenchyma and 1 sample from the cord and membranes. Supplementary samples were taken when gross lesions were present. After embedding the tissue samples in paraffin, 3-μm sections were cut using a microtome and stained with hematoxylin and eosin. Stained tissue sections were systematically reviewed by 2 pathologists, who were instructed to note the presence or absence of excessive syncytial knots (clusters of syncytiotrophoblasts), villous fibrosis, avascular terminal villi, chronic villitis (defined by lymphocytes and histiocytes in the villous axis), and intervillous lesions (defined by histiocytes in the intervillous space). Villous hypermaturation was assessed according to whether intermediate or terminal or both types of villi were found. The presence of decidual vasculopathy was defined by the presence of muscle in the spiral vessels, fibrinous necrosis, atheromatous lesions characterized by foamy macrophages, or thromboses in the vessels of the basal plate. Circulating erythroblastosis was defined as the presence of nucleated red blood cells in small-caliber placental vessels. Deposits of intervillous fibrin were recorded only when they were large (>20%), occupying the entire intervillous space and encompassing necrotic villi. Inflammation of the basal plate was diagnosed when plasma cells were observed at this site. Inflammation of the chorionic plate (acute chorioamnionitis) was noted when polymorphonuclear neutrophils were observed in both the chorionic plate and the membranes [7,9].

Data were analyzed in a 2-stage process using Stata version 8.2 (StataCorp, College Station, TX, USA). First, each variable was independently compared between the 2 groups using the χ^2 test for matched pairs. Next, the gross and microscopic variables that were significantly associated with pre-eclampsia ($P<0.05$) were entered into a forward stepwise logistic regression model that allowed the existence and strength of the association of each type of lesion with pre-eclampsia to be examined. In order to rank these variables, gross and microscopic lesions were first considered separately and then combined into a single logistic regression model.

3. Results

The characteristics of the pre-eclampsia and control groups are presented in Table 1. The mean age of the women was not significantly different between the 2 groups. Gestational age at delivery ranged from 23 to 41 weeks, with a mean of 31.6 weeks in both groups. The proportion of nulliparous women was significantly higher in the pre-eclampsia group than the control group (69.4% vs 32.4%; $P<0.001$). The pre-eclampsia group included 54 cases of HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome; by contrast, no cases of HELLP syndrome were reported in the control group ($P<0.001$). The mean birth weight was 230 g lower in the pre-eclampsia group than in the control group ($P<0.01$), and approximately one-third of the pre-eclampsia group recorded a birth weight below the third percentile for gestational age (30.0% vs 7.5%; $P<0.05$) [10].

Gross examination of the placenta (Table 2) showed a significantly lower mean placental weight for the pre-eclampsia group versus the control group (mean difference, 80 g; $P<0.001$). Low placental weight was more frequent among women with pre-eclampsia than among the matched controls (13.3% vs 1.2% for a weight decrease ≥40%; $P<0.001$). In all, 35.3% of women with pre-eclampsia had at least 4 placental infarcts, compared with just 2.3% of women in the control group ($P<0.001$). Pre-eclampsia was also significantly associated with the presence of a high frequency of retroplacental hematomas (12.1% vs 2.3%; $P<0.001$) and with a low rate of subchorionic thrombosis (6.9% vs 14.5%; $P<0.05$). No other gross abnormalities were significantly associated with pre-eclampsia. The overall rate of no gross placental abnormalities detected was 13.9% in the pre-eclampsia group and 44.5% in the control group ($P<0.001$).

Table 1
Characteristics of the study population.[a]

Characteristic	Pre-eclampsia group (n = 173)	Control group (n = 173)	*P* value
Maternal age, y	28.0 ± 5.8	28.4 ± 5.7	>0.05
Nulliparous	120 (69.4)	56 (32.4)	<0.001
HELLP syndrome	54 (31.2)	0 (0.0)	<0.001
Gestational age, wk	31.6 ± 4.0	31.6 ± 4.0	>0.05
Fetal weight, g	1460 ± 800	1690 ± 790	<0.01
FGR below 3rd percentile	52 (30.0)	13 (7.5)	<0.05

Abbreviations: FGR, fetal growth restriction; HELLP, hemolysis, elevated liver enzymes, low platelet count.
[a] Values are given as mean ± standard deviation or number (percentage).

Table 2
Gross and microscopic characteristics of the placentas.[a]

Characteristic	Pre-eclampsia group (n = 173)	Control group (n = 173)	*P* value
Gross			
Placental weight, g	280 ± 150	360 ± 160	<0.001
Low placental weight			<0.001
<20%	91 (52.6)	152 (87.8)	
20–39%	59 (34.1)	19 (10.9)	
≥40%	23 (13.3)	2 (1.2)	
Number of infarcts			<0.001
0	59 (34.1)	150 (86.7)	
1–3	53 (30.6)	19 (10.9)	
≥4	61 (35.3)	4 (2.3)	
Retroplacental hematoma	21 (12.1)	4 (2.3)	<0.001
Marginal hematoma	29 (16.7)	42 (24.2)	0.08
Subchorionic thrombosis	12 (6.9)	25 (14.5)	<0.05
Intervillous thrombosis	19 (10.9)	12 (6.9)	0.19
No gross lesions	24 (13.9)	77 (44.5)	<0.001
Microscopic			
Absence of intermediate villi	124 (71.7)	28 (16.2)	<0.001
Presence of terminal villi	169 (97.7)	145 (83.8)	<0.001
Villous fibrosis	11 (6.4)	0 (0.0)	<0.001
Erythroblastosis	19 (10.9)	6 (3.5)	<0.01
Avascular terminal villi	16 (9.2)	5 (2.9)	<0.05
Villitis	4 (2.3)	7 (4.0)	0.36
Intervillositis	3 (1.7)	2 (1.2)	0.65
Intervillous fibrin	13 (7.5)	5 (2.9)	0.05
Increased syncytial knots	156 (90.2)	16 (9.2)	<0.001
Decidual vasculopathy[b]	88 (50.9)	14 (8.1)	<0.001
Basal-plate inflammation	63 (36.4)	38 (22.0)	<0.01
Chorionic-plate inflammation	5 (2.9)	32 (18.5)	<0.001
No microscopic lesions	5 (2.9)	101 (58.4)	<0.001
No gross or microscopic lesions	0 (0.0)	55 (31.8)	<0.001

[a] Values are given as mean ± standard deviation or number (percentage).
[b] Persistence of spiral arterioles (7.2% vs 1.1%; $P<0.01$); fibrinoid necrosis (30.8% vs 5.8%; $P<0.01$); atheroma (5.8% vs 0.0%; $P<0.01$); and thrombosis of uteroplacental vessels (8.2% vs 2.1%; $P<0.05$).