Placental vascular lesion differences in pregnancy-induced hypertension and normotensive fetal growth restriction

Michal Kovo, MD, PhD; Letizia Schreiber, MD; Avi Ben-Haroush, MD; Suzanna Wand, MD; Abraham Golan, MD; Jacob Bar, MD, MSc

OBJECTIVE: Pregnancy-induced hypertension/preeclampsia (PIH) and fetal growth restriction (FGR) share a common placental origin. The pathologic classification that divides placental lesions to maternal or fetal origin was compared between these disorders.

STUDY DESIGN: Placentas from pregnancies that were complicated by PIH, normotensive FGR, or by both (combined) were analyzed, and lesions were classified as those consistent with maternal under-perfusion and with fetal thromboocclusive disease.

RESULTS: Maternal vascular lesions were more common in the PIH group and combined group (61% and 59%, respectively), compared with the FGR group (16.2%; P < .001), and villous lesions were more common in the combined group, compared with the FGR and PIH groups (79.5%, 53.5%, and 46.9%, respectively; P = .004). Fetal villous changes were observed in 16.2% in the FGR group, compared with 3.1% in the PIH group (P = .03), and chronic villitis was 15.2% in the FGR group vs 1.6% in the PIH group (P = .004).

CONCLUSION: Placental lesions correspond with different clinical presentations.

Key words: fetal growth restriction, hypertension, placenta, underperfusion, villous lesion

both in the search for a possible placental fetal origin component for these disorders.

Materials and Methods

Study design

The medical records of all patients who had PIH/preeclampsia (PIH group) or normotenstive FGR (FGR group) or whose condition was complicated by both (combined group) and their placentas underwent histopathologic examination and were included in the study, which was conducted in the Department of Obstetrics and Gynecology, Edith Wolfson Medical Center in Holon, Israel, from January 2006 to December 2008. The information that was collected included maternal characteristics such as age, gravidity, parity, cigarettes smoked (per day), known chronic disease as pregestational diabetes mellitus (DM; type 1 and 2), thrombophilia, epilepsy, asthma, and chronic pharmacotherapy, which was defined as medical treatment received by the patient during whole pregnancy, except vitamin or iron supplements. In addition, data concerning pregnancy follow-up evaluation, complications that developed during pregnancy (such as gestational DM [GDM] A1 and A2) and mode of delivery, were also recorded. At birth, all neonates were examined by pediatricians. Birthweights and the specific percentiles for weight were assigned with the updated Israeli growth charts. Exclusion criteria included multiple pregnancies and pregnancies that were complicated with neonatal chromosomal or structural anomalies or by intrauterine infection. Approval for the study was obtained from the Local Ethics Committee.

Hypertensive syndromes in pregnancy were classified according to well-established characteristics such as laboratory and clinical criteria into gestational hypertension (PIH), chronic hypertension, and preeclampsia. FGR was defined when the actual birthweight was below the 10th percentile for gestational age. The gestational age estimation was based on the last menstrual period and validated by fetal ultrasound scanning that was performed in >90% of the women before week 13 of gestation in the study groups.

Collection and preparation of tissue

Placental pathologic examinations were performed according to a standard protocol. Placental weight was recorded, and its percentile was assigned based on specific placental weight charts. The fetoplacental weight ratio was calculated as the ratio between fetal birthweight to placental weight. Placentas were formalin fixed. From each placenta, 6 tissue samples were embedded in paraffin blocks for microscopic assessment: 1 role of the free membranes (chorion and amnion with attached deciduas capsularis) and a section of umbilical cord; 5 full-thickness disc samples (1 at the cord insertion, 1 in central tissue that appeared abnormal on gross examination, 2 from central tissue, and 1 at the margin of visible abnormal areas on gross examination). All pathologic examinations were done by a single pathologist. Placental lesions (which were considered in this work) were classified into maternal or fetal origin lesions. Maternal origin lesions included placental findings that were consistent with maternal underperfusion vascular and villous changes. Maternal origin vascular lesions included acute atherosis and mural hyper trophy; maternal villous changes included increased syncytial knots, villous agglutination, increased intervillous fibrin deposition, and villous infarcts. Placental fetal origin lesions, which were also consistent with the term fetal thromboocclusive disease, were divided into vascular and villous changes. Fetal origin vascular lesions were considered to be thrombosis of chorionic plate and stem villous vessels; villous changes included avascular villi. In addition, villitis of unknown cause or chronic villitis, which was defined as placental inflammatory changes in fetal blood vessels that were recorded separately.

Statistical analysis

Data are presented as mean ± SD or median and range as appropriate. Data analysis was performed with the SPSS software (version 15.0; SPSS Inc, Chicago, IL). Analysis of variance was used to compare independent nonparametric cetic variables among the 3 groups (PIH, FGR, and combined). A probability value of < .05 was considered significant.

Results

Of the 202 patients who were included in the study, 64 women (32%) were in the PIH group, 99 women (49%) were in the normotensive FGR group, and 39 women (19%) were in the combined group. Maternal characteristics are summarized in Table 1. Mean maternal age in the FGR group was significantly lower, 30.1 ± 5.5 years, compared with the PIH and combined groups (33 ± 5.4 and 32.8 ± 5.8 years, respectively). Gravidity and parity did not differ among the groups. Patients in the FGR group had a lower body mass index (22.5 ± 4.7 kg/m²), compared with the other 2 groups (PIH, 27.7 ± 8 kg/m²; combined, 26 ± 6.5 kg/m²; P < .001). This difference in body mass index remained after the exclusion of women with GDM and pregestational DM from the study groups (P = .001). The rate of the different hypertensive disorders was significantly higher in the PIH and combined groups, as expected from the study design. The rate of other maternal chronic disease (asthma, epilepsy, hypothyroidism) was similar in the 3 groups; however, DM (GDM and pregestational DM) was significantly higher in the PIH group (25%), compared with the FGR and combined groups (3% and 5.3%, respectively). There was no significant difference in pregestational DM in the PIH (3.1%), FGR (0), and combined (2.5%) groups. The rate of thrombophilia was not significantly different among the study groups (1.6%, 3%, and 2.6% in the PIH, FGR, and combined groups, respectively).

Gestational age at delivery was significantly lower in the combined group (34 ± 4 weeks) compared with the FGR and PIH groups (38 ± 2.2 and 36.6 ± 3 weeks, respectively). Birthweight percentile was significantly lower in the FGR and combined groups (5.3% ± 2.4% and 5.7% ± 2.8%, respectively) compared with the PIH group (46.5% ± 28.5%), as expected from the study design.

Placental characteristics are summarized in Table 2. Mean placental weight that was adjusted for gestational age was
significantly lower in the FGR and combined groups, compared with the PIH group ($P < .001$). In addition, the rate of placental weight <10th percentile was significantly higher in the FGR and combined groups (41.4% and 64.1%, respectively), compared with the PIH group (14.1%; $P < .001$). The fetoplacental weight ratio was the highest in the FGR group (6.4 ± 1.3), compared with the PIH group (6.0 ± 1.8) and the combined group (5.4 ± 1.4; $P = .005$).

The rate of retroplacental and marginal hemorrhages was similar among the groups. Maternal origin vascular lesions (Figure 1, A) were present in 60.9% of the placentas in the PIH group and in 59% of the combined group, compared with only 16.2% in the FGR group ($P < .001$). Maternal origin villous lesions (Figure 1, B) were significantly more common in the combined group, compared with the FGR and PIH groups (79.5%, 53.5%, and 46.9%, respectively; $P = .004$). Fetal origin villous changes (Figure 2) were significantly higher in the FGR and the combined groups (16.2% and 10.3%, respectively), compared with the PIH group (3.1%, $p=0.033$). No significant difference was
In the present study, differences in the morphologic appearance of placentas from pregnancies that were complicated by hypertensive disorder and/or FGR were observed. Initially, FGR pregnancies were associated with significantly lower placental weight and lower placental weight percentile ratio, regardless if pregnancy was further complicated by PIH, compared with pregnancies that were complicated by PIH alone. This finding is in concordance with previous stereologic investigations of placentas. In addition, we found that placental lesions, which were defined as maternal vascular lesions, were more common in pregnancies that were complicated by hypertensive disorders, compared with pregnancies that were complicated by normotensive FGR. This association between abnormality of the maternal side of the placental circulation, which is often a result of arteriopathy, and PIH or FGR is well-established in the literature. We have also found that most of the placentas with PIH/pre-eclampsia (61%) showed direct maternal vascular changes that were the result of under-perfusion. These results differ from a previous study that demonstrated maternal vascular changes only in 24% of placentas from pregnancies that were complicated by PIH. Although PIH is primarily an impairment of the maternal circulatory system that is believed to be the result of early developmental events that lead to inadequate vascular remodeling and/or structural abnormalities of maternal arteries, these placental lesions are known to be nonspecific and are associated with other pregnancy complications.

On the other hand, we found that, in pregnancies that are complicated by normotensive FGR, placental fetal villous changes that are also consistent with the term fetal thromboocclusive disease were present more than in pregnancies that were complicated by PIH alone. Although we could not observe any difference in the appearance of direct fetal vascular lesions, placental findings that are considered to be of fetal origin, such villous changes (chronic villitis or villitis of unknown cause) were predominant in the FGR group.

The present study is unique in several aspects: (1) we directly compared distinct pathologic lesions to different clinical entities that are known to be associated with placental vascular compromise (PIH and FGR). There are many other studies on placental findings in pregnancy complications by PIH and FGR, but the comparison between these entities was not described in detail. (2) We used the placental finding criteria that had been validated and adapted by the Society for Pediatrics Pathology, which methodically differentiates between the different pathologic processes (maternal vascular under-perfusion and fetal vascular obstruction caused by a lack of uniformity in diagnostic criteria, grading, and scaling of these lesions in the different studies). (3) The placental fetal component of the different entities was investigated by us and less by other investigators and may contribute to the lack of knowledge on the significance of placental fetal origin changes in respect to clinical manifestation of PIH and/or FGR. (4) Our findings suggest that different placental lesions, whether from maternal or fetal origin, are associated with the corresponding clinical presentation, hypertensive disease, or FGR. (5) To the best of our knowledge, we are the first to demonstrate that the placental fetal component is more common and that the placental maternal component is less common in pregnancies that are complicated by FGR, compared with those pregnancies that are complicated by...
PIH. Moreover, in addition to chronic villitis that was found more often in FGR placentas by us and also shown by other investigators, 27-29 our finding of the dominance of villous changes in FGR has not been described before.

Distinct pathologic lesions that are related to fetal vascular obstruction have long been recognized. 30-32 Fetal vascular obstructive lesions are probably the result of stasis, hypercoagulability, and vascular damage within the fetal circulation, and because obstruction and low fetal blood flow in the absence of thrombosis also causes downstream effects, it is believed that villous changes are a more sensitive criterion to make the diagnosis of chronic fetal vascular obstruction and are more reproducibly diagnosed than lesions of large vessels. 33 It should be emphasized that acute atherosis and recent fetal thrombi, which are more acute vascular lesions, are not always accompanied by downstream chronic villous changes.

We are aware of our study limitations. First, placental weight and percentile could have been influenced by significantly lower maternal body mass index in the FGR group, which suggests that constitutional factors contributed to the smaller placentas and the low birthweights; on the other hand, more common GDM in the PIH group influenced the higher placental weight in this group. Second, the FGR group was heterogeneous, because selection was according to fetal birthweight (<10th percentile) without the use of additional tools, such as Doppler blood flow velocity studies to isolate those pregnancies with placental insufficiency.

In summary, the predominance of the pathologic placental fetal origin lesions in pregnancies that were complicated by FGR, compared with placentas from pregnancies that were complicated by hypertensive disorders, may indicate that placental lesions correspond with the different clinical presentations.

REFERENCES