Pathological Changes in Placentas from Pregnancies with Preeclampsia and Eclampsia with Emphasis on Persistence of Endovascular Trophoblastic Plugs

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Aim To assess the frequency and types of histopathological changes in placentas from pregnancies complicated by preeclampsia/eclampsia.

Methods Placentas routinely sent for pathological examination (n=1,689) were studied microscopically and compared to findings of 50 placentas from uncomplicated pregnancies.

Results Out of 1,689 placentas from singleton pregnancies, 279 (16.5%) were from pregnancies complicated by preeclampsia/eclampsia. Seventy five placentas (26.8%) were appropriate for gestational age; other findings included: infarcts of various stage and volume in 63 cases (22.6%), minimal hypoxic damage in 27 cases (9.7%), accelerated maturation in 42 cases (15.1%), chronic villitis in 18 cases (6.5%), mixed findings in 18 cases (6.5%), intervillous thrombosis in 15 cases (5.4%), subchorial thrombosis in 9 cases (3.2%), immaturity of the villi in 6 cases (2.1%), and findings suggestive of placental insufficiency in 6 cases (2.1%). Normal findings were significantly more frequent in the control group (P<0.001), but no other significant differences between the groups were found. In 4 (1.4%) placentas from pregnancies complicated by preeclampsia/eclampsia (gestational age 32 to 36 weeks), remnants of endovascular trophoblastic plugs in the vessels of the basal decidua were found.

Conclusion No significant difference was found between the group of placentas from pregnancies complicated with preeclampsia/eclampsia and the control group with regard to ischemic changes of the placenta. Endovascular trophoblastic plugs in the basal plate vessels from the third trimester placentas may play an additional role in the development of ischemic lesions in the placentas from pregnancies complicated with preeclampsia/eclampsia, but may also simply represent indirect evidence of the abnormal expression of certain adhesion molecules in this disorder.

During the physiological changes that occur in the first and in the beginning of the second trimester of pregnancy, spiral arteries of the placental bed are converted into the uteroplacental arteries (1-3). The essence of this conversion consists of losing the muscular elements in the vessel walls, making them unable to respond to vaso-motor influences. Cells that infiltrate the walls of spiral arteries and replace their normal elements are called migratory, non-villous, or intermediate trophoblastic cells (3,4). Beside infiltrating and replacing the anatomic structures of spiral arteries, intermediate trophoblastic cells also penetrate into the lumina of these vessels, forming endovascular plugs. These plugs are one of the reasons why early uteroplacental blood flow cannot be visualized, even with transvaginal ultrasound, during the first 12 weeks of gestation (5). In uncomplicated pregnancies, the endovascular trophoblast is bound to disappear by the end of the second tri-
mester of pregnancy, but the literature about this topic is scarce (6). Some studies, especially those dealing with the morphological analysis of placental bed, have recorded a partial or complete lack of physiological changes (ie replacement of just a part of vessel wall circumference, or findings of physiological changes only in decidual, but not in the inner myometrial portion of spiral arterioles) in uteroplacental vessels in pregnancies complicated by preeclampsia or eclampsia (7-9). In some vessels that have not undergone physiological changes, acute atherosis was noticed (7-10). When the whole placentas are examined, these changes are also noticed in the basal plate and especially in the amniochorial membranes (because physiological changes in the blood vessels are not developed there, due to the lesser degree of invasion of intermediate trophoblast) (9).

Here we describe another pathomorphological feature, persistent endovascular trophoblastic plugs. It can sometimes be observed in vessels of the placental bed of third trimester placentas, in pregnancies complicated by preeclampsia and eclampsia.

Material and Methods

During 1998-2002, 1,689 placentas from singleton pregnancies were consecutively sent for routine pathological examination. In 279 cases, the placentas were examined by a pathologist because of preeclampsia or eclampsia, defined by the obstetricians as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mmHg (18.7 kPa or 12.0 kPa, respectively) measured at least twice and proteinuria of 300 mg/24 h or 300 mg/L with or without edema. The placentas were weighted immediately after delivery and examined by a pathologist (M. K. or Lj. H.), sectioned serially at 5-10 mm intervals, and 5-10 samples of the full placental thickness were taken for histopathological examination, as well as the sample of placental membranes. The membranes were stripped from the placental surface, and rolled so that the transverse cut for histologic sample was obtained. Two samples of the umbilical cord (from the placental and fetal ends) were also taken for histological examination. The samples were processed routinely, for paraffin embedding, cut at 5 μm, stained with hematoxylin-eosin and periodic acid-Schiff (PAS) stains, and examined by light microscopy (M. K. and Lj. H.). Histopathological findings were roughly divided into those adequate for gestational age, those with infarcts (of different age and extension), minimal hypoxic damage (characterized by circular cytotrophoblastic proliferation, basal membrane thickening, and excessive number of syncytial knots at the surface of most chorionic villi), accelerated maturation of placental villi, chronic villitis, mixed histological findings (normal villi, those showing accelerated maturation and edematous villi), intervillous thrombosis, subchorial thrombosis, immaturity of the villi, and findings suggestive of placental insufficiency (unexplained villous fibrosis combined with any of the above mentioned findings). Results of the pathological examination were compared with a control group of consecutively examined 50 placentas from uncomplicated singleton pregnancies with gestational age ranging from 29 to 40 weeks. In cases of premature delivery, all placentas showing signs of inflammation of the membranes were excluded from the study, which left only placentas from premature deliveries due to cervical insufficiency or otherwise unexplained cause. The maturity of the placental tissue was assessed according to gestational age.

For statistical analysis, χ²-test was used. We used statistical software Analyse-it, version 1.71 (Analyse-it Software, Ltd, Leeds, UK) for Microsoft Excel for Windows.

Results

We analyzed 279 placentas from pregnancies complicated by preeclampsia or eclampsia. They constituted 16.5% of 1,689 consecutively routinely examined placentas during the period from 1998 to 2002. In 127 cases (45.5%), the diagnosis of hypertensive disorder of pregnancy was not the only one; 63 (22.6%) of the total number of placentas were also associated with the diagnosis of intrauterine growth retardation (IUGR) of the fetus. The mean gestational age was 36.4±3.5 weeks, whereas in control group it was 38.2±2.7 weeks (χ²1 = 0.503, P = 0.478). Six placentas (2.2%) were from pregnancies ending before 28 gestational weeks; 120 placentas (43%) were from pregnancies ending between 28 and 37 gestational weeks, and 153 placentas (54.8%) were from term pregnancies. The mean placental weight was 483.4±173.4 g, compared with 512.5±83.1 g in the control group (χ² = 0.544, P = 0.393). Figure 1 shows the histopathological findings...
findings of placentas from pregnancies complicated by hypertensive disorders of pregnancy in comparison with the findings in the control group. In the group of normal placentas, the number of normal findings was more frequent than in the group of placentas from pregnancies complicated by preeclampsia/eclampsia ($P < 0.001$). The difference between the number of other, even ischemic changes between the investigated and the control group was not significant. On gross examination, retroplacental hematoma was observed in 3/279 (1.07%) placentas. Acute atherosis of uteroplacental vessels was found in 8 cases (2.8%). In 3 cases, it was localized in placental membranes, and in 5 cases in the basal decidua. In 4/279 (1.4%) placentas, from gestation of 32 weeks and 4 days to 36 weeks and 2 days, trophoblastic plugs in the vessels of the basal decidua were found, either attached to the vessel wall (Fig. 2) or seemingly free in the lumen (Fig. 3). In all 4 cases, the pregnancy was complicated only by preeclampsia, and the overlying placental villi showed evidence of cytotrophoblastic proliferation and excessive formation of syncytial knots.

**Discussion**

The relative frequency of hypoxic changes and acute atherosis in the third trimester placentas from pregnancies complicated by preeclampsia/eclampsia was expected. However, we were surprised not to find significant difference between the appearance of pathological, primarily ischemic changes in the investigated and in the control group, especially since findings of more frequent ischemic changes in placentas from pregnancies complicated by preeclampsia/eclampsia have been published before (6,11). Perhaps the explanation may be due to the fact that about a quarter of the cases in this study were complicated not only by hypertensive disorders but also by diabetes mellitus. Placentas from diabetic pregnancies are characterized by villous immaturity, chorangiosis, and fibrinoid necrosis rather than ischemic changes, but if diabetes was appropriately controlled and treated during pregnancy, the findings may also be normal (6,12). We also found no significant difference in placental weight between the investigated and the control group. Rolled up strips of the placental membranes proved to be a valuable source of decidua vera containing portions of spiral arteries which may show acute atherosis. This was confirmed in this study, because in 3 out of 8 cases of diagnosed acute atherosis, these changes were found in the decidual...

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**Figure 1.** Histopathological findings of placentas from pregnancies complicated by preeclampsia/eclampsia (closed bars, n=279) in comparison to the findings in the group of placentas from uncomplicated pregnancies (open bars, n=50). Asterisk indicates $P<0.001$.

**Figure 2.** Endovascular trophoblastic plug (arrow) attached to the vessel wall in the basal plate of the third trimester placenta (hematoxylin-eosin, ×100 magnification).

**Figure 3.** Endovascular trophoblast free in the vessel lumen in the basal plate of the third trimester placenta (hematoxylin-eosin, ×100 magnification).
layer of the membranes. The latter was histopathologically characterized by fibrinoid necrosis, perivascular mononuclear infiltrate, and infiltration by lipophages. The etiology and pathogenesis of acute atherosis are still unclear, but its similarity to vascular lesions in allograft rejection reaction according to some authors suggests the involvement of the immune system (13,14). The fact that it appears in vessels without physiological changes of pregnancy explains the more frequent formation of luminal obstruction or thrombosis and subsequent hypoxic changes of placental tissue.

The most unexpected findings in this study were the endovascular trophoblastic plugs in the vessels of the basal plate of placentas from the third trimester of pregnancy. To the best of our knowledge and scarce data from the literature, these plugs should have disappeared by the third trimester (6,15). Currently, there are three hypotheses that try to explain the formation of endovascular plugs. The first, known as the extravasation hypothesis, suggests that endovascular trophoblast derived from an unknown source gains access to the arterial lumens via or close to their point of confluence with the intervillous space and then migrates along the arterial lumens, retrograde to blood flow, by adhering to and replacing endothelium, locally forming intraluminal trophoblastic plugs; some of these cells leave the lumen and centrifugally invade media and adventitia (16). However, the study that proposes this hypothesis was based only on rhesus monkey placentas (16). The second, known as intravasation hypothesis, is based on studies of human placentas and favors the concept according to which the endovascular trophoblast represents an end stage of differentiation of interstitial trophoblast whose subpopulation invades the arterial wall from the outside (17,18). The third hypothesis, by Kam et al (19), is the combination of the two. In any case, the trophoblast that invades arterial walls and forms endovascular plugs originates from the cell columns that connect anchoring villi to the basal plate (20). In the rhesus monkey, the endovascular trophoblast was shown to maintain proliferation, representing a self replicating population in those stages of pregnancy when trophoblastic shell no longer exists (21). Proliferation of endovascular trophoblast in humans has not been observed (22), but we cannot exclude the possibility that it continues until the late stages of pregnancy, contribut-
cytokines that cause unsatisfactory physiological change, there could also be overexpression of other adhesion molecules, preventing the endovascular plugs to disengage from the vessel wall and disappear, either by apoptosis or by digestion by macrophages. Although at this moment we do not have a solid proof for this hypothesis, circumstantial evidence speaks in its favor.

Endovascular trophoblastic plugs in placentas from the late second and the third trimester of gestation have been, to the best of our knowledge, mentioned only in the study by Khong et al (9) as an incidental finding. They found endovascular trophoblast in 8 out of 29 (27.6%) placentas from pregnancies complicated by preeclampsia and small for gestational age infants either free in the lumen or more often attached to the intima. The gestation ranged from 28 to 38 weeks, but it is not clear whether all these findings were in the samples from the placental bed (sampled after cesarean hysterectomy in 2 cases of preeclamptic and 7 cases of normal pregnancies, and biopsied in 94 cases from normal and abnormal pregnancies) or some of them were in the placental bed plate from the delivered placenta (sampled in 69 cases). The study of Khong et al, offered no explanation for this phenomenon (9). Our series revealed endovascular plugs in only 1.4% placentas. In comparison to the findings of Khong et al (9), this percentage was strikingly lower. This difference could be explained by the fact that they examined more samples from placental bed biopsy than from the whole placentas, and in their work did not clarify whether the plugs were found in placental bed biopsies or in the basal plate of the entire placentas, whereas we examined the placentas routinely, taking the routine number of samples from a relatively large area of the whole basal plate. In this way, we could have missed a certain number of plugs.

In conclusion, this study showed that in some placentas from pregnancies complicated by preeclampsia and eclampsia, the endovascular trophoblastic plugs remained until the third trimester of pregnancy, possibly contributing to the ischemic damage of placental tissue. On the other hand, there is a possibility that endovascular trophoblastic plugs do not contribute significantly to ischemic damage of the placenta in pregnancy complicated by preeclampsia/eclampsia, but simply reflect disregulated cell to cell interactions in this pregnancy disorder.

References

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Received: February 15, 2005
Accepted: April 4, 2005

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