

Background and Relevance of Studying Morphological Changes in the Placenta during the Critical Period of 20-24 Weeks

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Abstract: An article on the structure of the human placenta at 20-24 weeks of pregnancy emphasizes the importance of its features in connection with the differentiation of chorionic villi. Villous transformation, reduction of the barrier between maternal and fetal blood flow, and changes in placental morphology in preterm pregnancy were the main topics of discussion. Italian researchers found that the placenta in pregnancies of women aged 20-24 years was burdened with hyperplasia, a stromal component and other pathological changes, which can lead to various disorders in the fetus. Additionally, a study by researchers from Wayne State University of Michigan in the US discusses the association of maternal plasma angiogenic index with fetal death >24 weeks, suggesting its use in predicting such cases. This metric had a significant positive coefficient for predicting fetal death and was also associated with a variety of adverse fetal outcomes. The article also describes placental abnormalities associated with stillbirth and establishes the importance of identifying infants with fetal growth restriction (SGA), which is associated with reduced perinatal mortality. However, she also discusses the limitations of existing tests and methods for identifying children with SGA, highlighting the need for further research in this area.

Keywords: early preeclampsia; fetal growth restriction (SGA), late-onset preeclampsia; microRNA; placenta; second trimester; morphology of placentas; pathology of the placenta, chorionic villi, syncytiocapillary membranes.

Relevance

The structure of the human placenta at different stages of pregnancy has its own characteristics due to the gradual differentiation of chorionic villi. During the process of villous transformation, the barrier between maternal and fetal blood flow decreases due to thinning of the syncytiotrophoblast, a decrease in the number of cytotrophoblast cells and a decrease in villous diameter. In addition, the fetal capillaries move closer to the surface of the villi, thereby reducing the diffusion distance, which is especially necessary during childbirth. During premature pregnancy, various disorders of chorionic villi differentiation are observed, there are no terminal differentiated villi and, as a result, the number of syncytiocapillary membranes sharply decreases. "Efficiency of the placenta" is largely associated with early angiogenesis, since as soon as a decrease in placental blood flow and the predominance of avascularized terminal villi sharply reduce compensatory capabilities and contribute to abortion. But, of course, the placenta has a significant functional reserve, which is demonstrated by the variety of morphological changes at different stages of gestation and with various extragenital pathologies. Later disturbances in the morphology of the placenta, microinfarctions, edema, fibrinoid deposition, necrosis of individual villi do not lead to fatal consequences (Zenkina V.G. et al. 2017).

Italian scientists Saha S., Biswas S (2014) note that the placenta born at 20-22 weeks of pregnancy, burdened with various extragenital pathologies (hypertension, diabetes mellitus, hepatitis), is characterized by a predominance of hyperplastic villi, dominance of the stromal component, and narrowing of the main vessels in stem villi due to wall hyperplasia, deficiency of intermediate differentiated and terminal villi, a decrease in the specific gravity of blood vessels, and, consequently, hypoplasia of capillaries and syncytiocapillary membranes. In some cases, the villi have irregular contours, cystic degeneration, increased fibrosis, fibrin deposits in large vessels, and pockets of avascularized villi. All these signs characterize the state of malperfusion, which significantly disrupts the main function of the placenta - trophic, and leads to various disorders in the fetus: extremely low

body weight, hypoxia, post-hypoxic encephalopathy and other disorders of the central nervous system. All of these changes are usually included in the clinical practice of obstetricians under the term “placental insufficiency,” which is usually determined by indirect methods based on fetal morphometry.

The authors Dagklis T assess the influence of placental laterality at 20-24 weeks of gestation on Doppler indices of the uterine arteries, fetal growth and preeclampsia, Tsakiridis I. (2022). Study of singleton pregnancies aged 20 to $<$ years+0 and 23+6 gestational weeks resulting in a live birth for which placental site (posterior, anterior, diurnal, forearm, right lateral or left side) and bilateral uterine artery pulsatility index measurements were recorded (PI). The effect of placental location on the offspring's mean birth weight (BW) and PI z-scores was assessed using t -tests or ANOVA and post-hoc tests, as appropriate. The uterine artery pulsatility measurements of pregnant and preeclamptic patients were then grouped into three categories (normal mean PI; unilaterally increased mean PI; increased mean PI), and the odds ratio (OR) of unilaterally increased or increased mean PI compared with the normal mean was then calculated. PI for PE, BW <10th centile and BW <5th centile. Logistic regression then assessed the independent association of placental location, UtA PI category (normal mean, unilateral increase with normal mean, increased mean PI), and UtA PI z-score with PE, BW <10th centile, and BW <5th centile centile. The analysis included 5506 pregnancies. Lateral placenta was associated with higher mean PI z-score ($p = .003$) and lower BW ($p = 4.3$) than nonlateral placenta. Compared with normal mean PI IMA, unilaterally elevated PI with normal mean was associated with an increased risk of developing PE (OR 95.1, 9% CI 9.7–10.1), BW <7th centile (OR 95.1, 3% CI 2.4-5.1) and BW <8th centile (OR 95.1, 1% CI 2.9-10.5). Similarly, increasing mean UTA PI was also associated with an increased risk of PE, BW <9th, and BW <1st centile (OR 95.4, 8% CI 17.3–4.4; OR 95.3, 5% CI 5.7–7.0; OR 95.5, 1% CI 9.6– $<$, $>$ respectively). When assessing the independent association of placenta location and PI UtA with pulmonary embolism and low BW, only average PI UtA remains a significant prognostic factor. The authors state: Lateral placenta is associated with higher mean UtA PI and lower BW. Unilaterally elevated IMA PI still carries a greater risk of PE and low BW than bilateral normal PI, but this effect appears to be ultimately mediated by the mean UtA PI z-score, which is relatively elevated in these cases.

Predicting fetal death using a simple maternal blood test at 20-24 weeks: the role of angiogenic index-1 is considered by scientists from the Department of Obstetrics and Gynecology, Wayne State University Michigan USA Chaiworapongsa T, Romero R. (2017). 4006 women with singleton pregnancies recorded at 6–22 weeks of gestation in a pregnancy biomarker cohort study. The placentas of all cases of fetal death were histologically examined by pathologists. There were 11 cases of fetal death and 829 controls with samples available for analysis between 24 and 28 weeks of gestation. Three fetal deaths occurred before 28 weeks' gestation and eight occurred at 28 weeks' gestation or later. However, the incidence of placental damage consistent with insufficient maternal vascular perfusion was 33.3% (1/3) among those who had fetal death before 28 weeks and 87.5% (7 of 8) of those who had this complication at age 28 or later weeks of pregnancy. The maternal plasma angiogenic index-1 value was below the 10th centile in 63.6% (7 of 11) of patients in the fetal death group and in 11.1% (92 of 829) of the control group. The Angiogenic Index-1 value was <2.5th centile in 54.5% (6/11) of cases of fetal death and in 3.7% (31 of 829) of the control group. Angiogenic Index-1 value <2.5I Centile had the highest positive likelihood ratio for predicting fetal death >24 weeks (14.6; 95% CI, 7.7–27.7) and relative risk 29.1 (95% CI, 8, 8–97.1), followed by sEng >97.5Icentile and PlGF/sEng <2.5I, both with a positive likelihood ratio of 13.7 (95% CI 7.3–25.8) and a relative risk of 27.4 (95% CI 8.2–91.2). Among women without fetal death whose plasma angiogenic index - 1 concentration ratio was below the 2.5th centile, 61% (19/31) developed preeclampsia or delivered a newborn SGA; When the 10th centile was used as a cutoff, 37% (34/92) of women experienced these adverse outcomes.

Hezell AE, Hayes DJ, (2019) Placental anomalies occur in 11–65% of stillbirths. Identification of FGR in utero is difficult. Small for gestational age (SGA) fetal growth restriction, assessed after birth, is the most commonly used surrogate for this outcome. The degree of fetal growth restriction is

associated with the likelihood of FGR; 30% of infants with birth weight < 10th centile are considered to be FGR, while 70% of infants with birth weight < 3rd centile are considered to have fetal growth restriction. It is important to note that SGA is the most significant antenatal risk factor for a stillborn baby. Correct identification of children with fetal growth restriction is associated with a reduction in perinatal mortality. However, currently used tests, such as symphyseal fundal height measurements, have low sensitivity and specificity for identifying children with fetal growth restriction.

Strøm-Roum EM, et al. (2013) authors conducted a population-based study examining paternal age, placental weight, and placental-to-birthweight ratio and included all singleton births after 22 weeks' gestation in the Norwegian Medical Birth Registry (n = 590,835) from 1999 to 2009. The mean placental weight and placental-to-birth weight ratio were compared between paternal age groups. The association of paternal age with placental weight was assessed using linear regression analysis, and adjustments were made for maternal age, birth weight, parity, offspring sex, gestational age at birth, maternal smoking, preeclampsia, maternal diabetes mellitus, and pregnancy after assisted reproduction technologies (ART). Pregnancies with fathers aged 20–24 years had a mean placental weight of 656.2 g [standard deviation (SD) 142.8], whereas pregnancies with fathers aged 67 years or older had an average placental weight of 8.160 g (SD 0.50). (P < 0.001). The average birth weight of the offspring for pregnancies with fathers aged 20–24 years was 3465.0 g (SD 583.8), and for fathers aged 3498 years or older, it was 9.621 g (SD 8.50) (P < 0.001). The placenta to birth weight ratios for the respective paternal age groups were 0.191 (SD 0.039) and 0.196 (SD 0.044) (<0.001). In multivariate linear regression analysis, placentas in pregnancies fathered by a man 50 years of age or older weighed 13.99 g [95% confidence interval (CI) 10.88–17.10] more than in pregnancies fathered by a father 20–24 years of age (P < 0.001) after adjusting for maternal age, birth weight, parity, offspring sex, gestational age at birth, and maternal smoking. preeclampsia, maternal diabetes mellitus and pregnancy after ART.

Purpose of the study

The purpose of this study is to study the structural features of the human placenta at different stages of pregnancy and the associated changes in the placenta with insufficient maternal vascular perfusion, as well as the possibility of using angiogenic index-1 as a prognostic biomarker to predict the risk of fetal death and fetal growth retardation.

The purpose of the study by the authors of the literature used:

1. The structural features of the placenta are described at different stages of pregnancy and with various extragenital pathologies, including hyperplastic villi, avascularized villi, as well as narrowing of the main vessels and capillary hypoplasia.
2. We analyzed 4006 pregnant women, including 11 cases of fetal death and 829 controls, and examined placental anomalies in 11-65% of stillbirths.
3. The relationship between a low angiogenic index-1 value and the risk of fetal death among women at different stages of pregnancy, as well as the relationship between fetal growth restriction (SGA) factor and perinatal mortality, was studied. The study found that a low maternal angiogenic index-1 value is associated with an increased risk of fetal death, especially after 24 weeks of pregnancy. It was also noted that the factor of fetal growth retardation is a significant antenatal risk for a stillborn child, and correct identification of children with this factor is associated with a decrease in perinatal mortality. The findings suggest the potential value of Angiogenic Index-1 in clinical practice for predicting the risk of fetal death and fetal growth restriction, and for further study of possible methods to prevent this adverse maternal and fetal outcome.

Materials and research methods

This review contains information collected by domestic and foreign authors on the formation and structure of the placenta in normal and complicated pregnancy, as well as during pregnancy after IVF. It also addresses issues of functional diagnostics of the state of the placental complex in vivo. When

writing the article, 50 literature sources were used, published in international citation databases such as Pubmed and Scopus, as well as materials published in the Russian Science Citation Index, fundamental research, monographs, and dissertation abstracts.

Pathomorphological features of the placenta at different stages of gestation

The human placenta of the hemochorial type provides a number of functions (gas exchange, transport, metabolic, protective, hormonal) necessary for the full development of the fetus. The main factors of placental insufficiency, the pathophysiological mechanism, can be broadly divided into disorders of blood flow and exchange capacity along the syncytiocapillary membranes of the fetal placental villi. We analyzed the structure of various types of chorionic villi, intervillous space and syncytiocapillary membranes, and the ratio of the stromal and vascular components. During the process of villous differentiation, the barrier between maternal and fetal blood flow decreases due to thinning of the syncytiotrophoblast, a decrease in the number of cytotrophoblast cells and the diameter of the villous. During premature pregnancy, various disorders of chorionic villi differentiation are observed, there are no terminal differentiated villi and, as a result, the number of syncytiocapillary membranes sharply decreases. "Efficiency of the placenta" is largely associated with early angiogenesis, since only a decrease in placental blood flow and the predominance of avascularized terminal villi sharply reduce compensatory capabilities and contribute to termination of pregnancy. The placenta has a significant functional reserve, as demonstrated by the variety of morphological changes at different stages of gestation. Later disturbances in the morphology of the placenta, microinfarctions, edema, fibrinoid deposition, and necrosis of individual villi do not lead to fatal consequences.

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The analysis included 5506 pregnancies. Lateral placenta was associated with higher mean PI z-score ($p = .003$) and lower BW ($p = 4.3$) than nonlateral placenta.

During a microscopic examination of the placenta L.I. Kondakova and co-authors found that in the main group it was observed in 50% of cases of dissociated maturation of chorionic villi, and in 50% - premature maturation, which is manifested by a significant predominance of the number of terminal villi and the appearance of multiple syncytio-capillary buds in 73% of cases. An uneven thickness of syncytiotrophoblast was revealed with the formation of syncytiocapillary membranes in 73% of cases. Involutive-dystrophic changes in the placenta are statistically significantly more common (92% of cases) in the main group: calcifications - in 72% of cases, thrombosis of the intervillous space - in 59%, single pseudoinfarctions - in 82%, which is a manifestation of placental aging. In the main group, circulatory disorders occur statistically significantly in 72% of cases, in 94% - fibrinoid deposition: in the intervillous space, Langhans striae surrounding the villi are located in the form of thin stripes, and in the area of the basal decidual membrane of the placenta, Nitabuch fibrinoid deposition is pronounced. The conclusion states: The morphological structure of the placentas of women with late premature birth is characterized by involutive-dystrophic changes, as well as the presence of

compensatory and adaptive reactions. These morphological changes in the placenta during late premature birth will make it possible to provide personalized assistance to women in subsequent pregnancies to prevent premature birth.

Conclusions

The study found that lateral placenta was associated with higher mean fetal circumference index (PI) z-score and lower fetal weight (BW) compared to nonlateral placenta. This is quite interesting, since the location of the placenta can influence the development of the fetus.

Now, with regard to morphological changes in the placenta in women with late premature birth, quite important pathological signs were found here, indicating structural changes. Dissociated maturation of chorionic villi and premature maturation were found in 50% of cases. In addition, uneven syncytiotrophoblast thickness and other changes indicating aging of the placenta were detected.

Italian scientists Saha S. and Biswas S. (2014) conducted a study which found that the placenta born at 20-22 weeks of pregnancy with various extragenital pathologies, such as hypertension, diabetes and hepatitis, has certain characteristics. These features include predominance of hyperplastic villi, dominance of the stromal component, narrowing of the main vessels in the stem villi due to mural hyperplasia, lack of intermediate and terminal villi, decreased vascular density, and hypoplasia of capillaries and syncytiocapillary membranes. In some cases, the villi have irregular contours, cystic degeneration, increased fibrosis, fibrin deposits in large vessels, and pockets of avascularized villi. All these changes indicate a state of malperfusion, which seriously impairs the trophic function of the placenta and leads to various disorders in the fetus, such as low body weight, hypoxia, posthypoxic encephalopathy and other problems with the central nervous system.

Another study by Dagklis T. and Tsakiridis I. (2022) assessed the effect of placental laterality at 20-24 weeks of gestation on uterine artery parameters, fetal growth and the development of preeclampsia. The study included pregnancies between 20 and 23+6 gestational weeks that resulted in a live birth. The location of the placenta was recorded and uterine artery pulsatility index values were measured. The results showed that lateral placenta was associated with higher mean pulsatility index and lower birth weight compared with nonlateral placenta. A unilateral increase in pulsatility index with a normal mean is also associated with an increased risk of preeclampsia and low birth weight. The analysis also showed that the independent association between placental location and uterine artery pulsatility index values remained only for the mean pulsatility index value. The authors conclude that a lateral placenta is associated with an increased pulsatility index value and low birth weight, while a unilateral increase in the index is associated. The effectiveness of the placenta is highly dependent on early angiogenesis, because a decrease in placental blood flow or the predominance of avascularized terminal villi significantly reduces compensatory capabilities and can lead to termination of pregnancy.

Our findings highlight the potential importance of further research in this area and may also lead to the development of personalized programs to help women in subsequent pregnancies to prevent preterm birth.

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