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Changes in placenteral angiogenesis moduling gene activity by intrauterin growth retardation

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Summary

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The intrauterine growth retardation is a pathology with a multifactorial background. As long as a wide range of learning materials are available about the environmental factors acting a part of this pathology, the obtainable learnings about the genetic aptitude are straitened. Since the placental malfunction is an often cause of the development an intrauterine retardation, the placenta and the samples retrieved from the placenta get a potential great importance for the investigations of genes, gene groups, come into question in relation of the predisposition.

From these genes, the ones with angiogenesis regulator activities get deep significance, since the pathologic functioning of the placenta tightly correlate with the accurate placental circulation and optimal blood flow. The biologic mechanism of vascularisation and angiogenesis based on the functional balance of the pro- and antiangiogenetic genes, and lead to the development of intrauterine retardation in case of the damage of this trim.

In view of the biologic role of the 2 investigated genes influencing the regulation of the angiogenesis, the placental overexpression of endoglin with antiangiogenetic effect cause malfunction in the placental tissue, which lead to the failure of the oxygenation. This hypoxigenization stimulate the increased placental VEGF-A expression, which try to repair the vascular background of the circulation based on its angiogenetic effect.

Further clinical features (severity of IUGR, gestation age at birth) could affect – with different extent – the operation of these 2 genes.

The placental-tissue genexpression examinations could predict in the first tierce of the expectant the further development of the clinical aspect with damning own or familiar anamnesis, or potentially with foreseeingly high environmental

risk. As in our days women going to be pregnant by ever later age, the chorionic villi examinations due to the higher risk of fetal chromosome-abnormalities could give a handle also for genexpression examinations, which could predict the potential later onset of intrauterine retardation. The examinations, which could analyse similarly the maternal serum in parallel to the placental gene expression activity of the related genes as the etiology factors responsible for the intrauterine retardation, could open new perspectives in the clinical use, as this method could give a chance to perform a widely available, non-invasive screening activity for this pathology.

INTRODUCTION

Pregnancy, the intrauterine development of the fetus is a complex physiologic process based on the balance of several factors. Slowdown of intrauterine growth is called intrauterine growth restriction (IUGR). This disorder is one of the most common and most important gestational diseases. It is important not only due to the higher rate of the accompanying perinatal morbidity and mortality, but its long-term, postnatal consequences presenting mainly as neurological deficiency.

Often placental insufficiency of unknown etiology can be identified as the reason for retardation in addition to maternal, fetal, and environmental factors. Among the maternal causes primarily the different maternal diseases should be mentioned that make difficult to carry out the pregnancy and may impair the intrauterine oxygen and nutrient supply of the fetus, however, adequate energy input and nutrition is also important. Among the fetal causes intrauterine infections should be emphasized in addition to congenital malformations. Environmental factors may be multiple: alcohol, nicotine or drug abuse, environmental ionizing radiation or chemical exposure are also substantial etiologic factors. The most common but scientifically the least elucidated factor is the placental insufficiency among all disorders that may correlate with abnormal placentation, inflammation of the placenta, partial placental abruption, but also disorders of the umbilical cord such as single umbilical artery.

The essential criteria of energy and oxygen supply required to the intrauterine growth of the fetus are ensured by the placenta, therefore, it must be regarded as the key organ of fetal growth. This complex process is under genetic-endocrine regulation. Genes playing role in this process take part in regulating several physiologic processes and the change of their function may lead to abnormal intrauterine growth. The essential criterion for the physiologic placental function is adequate utero-placental circulation, which closely correlates with the appropriate condition, extent, and function of the placental vessel network. My evaluations focused on the analysis of the placental expression of two angiogenic genes taking part in the intrauterine growth of the fetus, the vascular endothelial growth factor A (VEGF-A) and the endoglin genes; based on the evaluation of the expression activity of these genes and taking further clinico-demographic data into account several conclusions may be made in order to elucidate the underlying pathology of intrauterine growth restriction.

AIMS

The main aim of my study was to evaluate the angiogenic factors of the abnormal placental blood flow as the underlying cause of plancental insufficiency. With the assessment of the placental expression of a pro- and an antiangiogenic gene (VEGF-A and endoglin) from the most important ones I tried to elucidate the pathological changes of the placental angiogenesis. As several clinical data were available, the aim of my study was also to interpret the different gene expression results in respect of the clinical information and to set up potential hypotheses. Among these the maternal age, gestational age, sex distribution of newborns, change of maternal weight and Body Mass Index during pregnancy, type of delivery and potential imminent intrauterine asphyxia made a practice-centered interpretation of the gene expression results particularly possible.

The available sample size was adequate to statistically analyze my gene expression results compared to the sample size of similar studies in the literature, however, the statistical evaluation of the clinico-demographic data was performed primarily to characterize the examined population as the sample size did not make the epidemiological analysis of this type of data possible.

All gene expression results was interpreted in respect of the available clinical information.

I intended to answer the following questions based on my evaluations:

1. What placental gene expression value of VEGF-A could be measured in the tissue samples from the placenta of fetuses with intrauterine growth restriction and with eutrophic growth? How does the VEGF-A gene influence the placental angiogenesis if intrauterine retardation or physiologic development is present?
2. Was there any correlation between the placental VEGF-A gene expression and the degree of intrauterine growth restriction?
3. Was there any correlation between the placental VEGF-A gene expression and the gender of the fetus?
4. Was the value of VEGF-A gene expression influenced by the gestational age at birth in the event of intrauterine retardation? How could the change of gene expression related to the gestational age be explained if intrauterine growth restriction was present?
5. What value of placental endoglin gene expression could be measured in the samples from the placenta of fetuses with intrauterine growth restriction and with eutrophic growth? How does endoglin gene influence the placental angiogenesis if intrauterine retardation or physiologic development is present?

6. Was there any correlation between the placental expression of the endoglin gene and the severity of intrauterine growth restriction?
7. Was there any correlation between the change of the value of endoglin gene expression and the gender of the fetus?
8. Was the value of endoglin gene expression influenced by the gestational age at delivery in the event of intrauterine retardation? How could the change of gene expression related to the gestational age be explained if intrauterine growth restriction was present?
9. What was the ratio of severe (birth weight is 0 to 5 percentiles) and less severe (birth weight is 5 to 10 percentiles) intrauterine retardation?
10. What was the median value of gestational age if newborns with intrauterine retardation were born?
11. How was the sex distribution of newborns with intrauterine retardation?
12. Was there significant difference between the median value of women's age delivering fetuses with intrauterine retardation or eutrophic fetuses?
13. What was the frequency of Cesarean section in pregnancies with intrauterine growth restriction and eutrophic fetal growth?
14. What was the maternal weight and Body Mass Index increase during pregnancy in the event of intrauterine growth restriction and eutrophic fetuses?

PATIENTS AND METHODS

In our study we compared the VEGF-A and endoglin gene expression results from placental samples obtained during birth of 101 fetuses with intrauterine retardation to the expression value of control cases treated between January 1, 2011 and January 1, 2013 at Semmelweis University. The control group consisted of 140 newborns in whom no disorder, gestational disease or developmental pathology occured during the intrauterine development and whose intrauterine growth showed physiologic rate during the pregnancy and whose birth weight proved to be eutrophic. Several other clinical data were collected from the pregnant women both in the examined and the control group and later the data were analyzed alone, and also in relation to the gene expression results. All clinical data are summarized in Table 1. From the clinico-demographic data maternal age, gain in maternal weight and change of BMI (Body Mass Index) during pregnancy, birth weight of the pregnant woman can be highlighted as valuable clinical information. The diagnostic criterion of intrauterine growth restriction was the value below standard 10 percentiles of fetal weight by gender and gestational age. Severe intrauterine retardation was defined if fetal weight dropped below 5 percentiles by gestational age and sex; if the value was between 5 and 10 percentiles the intrauterine growth restriction was called less severe. In the establishment of the diagnosis the comparison of the diameter (BPD, OFD) and circumference of the fetal head, the fetal abdominal circumference (AC) to the corresponding data of eutrophic fetuses with similar gestational age was an important factor. The potential reason of intrauterine retardation chromosomal aberrations and other developmental pathologies of the fetus, maternal malnutrition, intrauterine infections, placental morphologic abnormalities and multiple pregnancies were excluded and our evaluations were focused only on cases resulting from placental insufficiency.

In the specific assessed cases decision about the type of delivery was made based on clinical information; no selection was made according to the type of delivery during the processing of the samples.

During the sampling from the placenta an approximately 2x2x2 cm (8 cm3) piece of tissue was collected that was stored on -70 ºC until gene expression testing was started.

Before the examinations detailed informed consent was taken from the pregnant women in every case and they confirmed their agreement to the study with their signature on the Informed consent form.

No.	Date of delivery	Mature	Preterm	IUGR	Mother's date of birth	Age at delivery
History of preterm delivery	Previous IUGR	Number of miscarriages	Causes of miscarriages	Genetic history	Contraception	Smoking (cigarette per day)
NT (mm)	MSAFP (MOM)	OGTT fasting (mM/L)	OGTT 2 h (mM/L)	Biochemical screening	CVS/AC	TORCH
Father's age	Mother's weight at the beginning of pregnancy (kg)	Mother's weight at the end of pregnancy (kg)	Weight gain (kg)	Height (cm)	BMI at the beginning	BMI at delivery
Type of delivery	Delivery complications	Gender of the newborn	Weight (gram)	Length (cm)	Circumference of the head (cm)	Circumference of the chest (cm)
Blood group	GBS	Last WBC	Last CRP	Number of previous pregnancies	Number of deliveries	Deliveries in detail
Alcohol	Medications	Food suppl.	Gestational pathologies	Gestational complications	Gestational age at delivery	Mother's internal or other diseases
Ultrasound	Mother's birth weight (g)	Father's date of birth	Weight percentiles	Apgar		

Table 1 Clinical information from pregnant women

RESULTS

3. Gene expression results (VEGF-A and endoglin genes)

i.) The VEGF-A gene expression was compared based on the evaluation of the placenta of 101 fetuses with intrauterine growth restriction and 140 eutrophic fetuses. In the placental samples of newborns with IUGR the VEGF-A gene was overexpressed compared to both applied control genes (β-actin; NADPH) (Ln 2α: 1.32 and 1.56).

j.) In pregnancies with intrauterine growth restriction the placental VEGF-A gene expression in female and male fetuses did not show significant difference related to the gender.

k.) The VEGF-A gene expression of placental samples from newborns in the range of 0 to 5 percentiles showed no significant difference compared to the newborns in the range of 5 to 10 percentiles (Ln 2α: 0.58 and 0.64) regarding the severity of intrauterine growth restriction.

l.) The placental VEGF-A gene was overexpressed in case of intrauterine growth restriction before the pregnancy week 33 compared to eutrophic fetuses (Ln2α: 1.09), just as in the event of intrauterine growth restriction between the pregnancy week 33 and 37 (Ln2α: 1.27), and after week 37 (Ln2α: 1.35).

m.) The endoglin gene expression was compared based on the evaluation of the placenta of 101 fetuses with intrauterine growth restriction and 140 eutrophic fetuses. In the placental samples of newborns with IUGR the endoglin gene was overexpressed compared to the control gene (β-actin) (Ln 2α: 1.69).

n.) In female and male fetuses with intrauterine growth restriction the placental endoglin expression did not show significant difference (Ln 2α: -0.16).

o.) The endoglin gene expression of placental samples from newborns in the range of 0 to 5 percentiles showed no significant difference compared to the newborns in the range of 5 to 10 percentiles (Ln 2α: -0.02) regarding the severity of intrauterine growth restriction.

p.) The placental endoglin gene was overexpressed in case of intrauterine growth restriction before the pregnancy week 33 compared to eutrophic fetuses (Ln2α: 1.18), just as in the event of intrauterine growth restriction between the pregnancy week 33 and 37 (Ln2α: 1.24), and after week 37 (Ln2α: 1.31).

4. Clinical results

The severity of intrauterine growth restriction

Based on birth weight the more severe form of intrauterine growth restriction (weight between 0 and 5 percentiles) could be confirmed in 30.7% of newborns (n=31), while the incidence of the milder disease (weight between 5 and 10 percentiles) was 69.3% (n=80).

Gestational age of newborns with intrauterine growth restriction at delivery

The median value of gestational age in pregnancies with intrauterine growth restriction at delivery was 36±3.02 weeks and in eutrophic pregnancies 38±1.76 weeks ($p>0.05$).

The sex distribution of newborns with intrauterine growth restriction and in the control group

The male:female ratio in the 101 fetuses with intrauterine retardation was 0.58 (female: 64, male: 37), while the same value in the control group was 1.09 (male: 73, female: 67).

The median value of the maternal age in intrauterine growth restriction and eutrophic fetal growth

The median value of the age of women delivering fetuses with intrauterine retardation was 30.82±4.34 years, while the same value in the control group was 31.45±3.12 years ($p>0.05$).

Type of delivery in intrauterine retardation and eutrophic fetal growth

In case of intrauterine retardation pregnancies ended with vaginal delivery in 38.6% (39 cases) and with C-section in 61.4% (62 cases). Among the 62 cases where C-section was performed in 41 cases (66.1%) imminent intrauterine asphyxia was the indication for the operation. In 38.7% (51 cases) of eutrophic pregnancies serving as control group C-section was performed, while in 89 cases (61.3%) there was vaginal delivery. In eutrophic fetuses C-section was performed due to imminent fetal asphyxia in 23 cases (45.2%).

Change of maternal weight and BMI during pregnancy in case of intrauterine retardation and eutrophic fetal growth

The weight gain and change of Body Mass Index (BMI) during pregnancy in women expecting fetuses with intrauterine retardation showed significant difference compared to the similar variants of pregnant women expecting eutrophic fetuses. The median value of the weight gain during pregnancy was 14.8 kg in pregnant women expecting eutrophic fetuses compared to the median weight gain of 10.9 kg of pregnant women expecting fetuses with intrauterine growth restriction ($p<0.05$). The change of the median value of the BMI was 5.3 in women expecting eutrophic fetuses compared to the 4.1 BMI in women expecting fetuses with IUGR ($p<0.05$).

CONCLUSIONS

15. Based on the evaluated samples the VEGF-A gene was overexpressed in the placental samples from newborns with IUGR compared to both applied control genes. If the rate of intrauterine development is physiologic when the placental blood flow is adequate, the function of pro- and antiangiogenic genes is balanced. In case of intrauterine retardation due to placental insufficiency this balance changes. Based on my findings the increase in placental expression of the VEGF-A gene resulting from intrauterine growth restriction is the response of the placenta to hypoxia, thus it is rather a consequence in the pathomechanism of IUGR than a cause.

16. The VEGF-A gene expression activity of placental samples from newborns in the range of 0 to 5 percentiles showed no significant difference compared to the newborns in the range of 5 to 10 percentiles regarding the severity of intrauterine growth restriction. It renders likely that maternal blood flow increases the placental VEGF-A gene expression activity and in this way the angiogenesis in order to compensate the

slower intrauterine development. However, the degree of growth restriction has no significant importance in this compensating mechanism anymore.

17. Based on my evaluations the placental VEGF-A gene expression in female and male fetuses in pregnancies with intrauterine growth restriction did not show significant difference related to the gender. The sex of the fetus has no considerable importance in the angiogenic compensation resulting from the placental circulatory insufficiency and the increase in VEGF-A activity.

18. It was found that the VEGF-A gene expression activity increased independently from gestational age in intrauterine growth restriction. Although the difference between the specific gene expression values did not proved to be significant, it cannot be left out of consideration that the degree of overexpression showed positive correlation with the gestational age. According to that the VEGF-A placental activity proved to be higher in pregnancies that ended closer to the full term.

19. The endoglin gene was significantly overexprssed in placental samples from newborns with intrauterine growth restriction. This refers to the presence of antiangiogenic effect in the placental tissue. Because of the disturbance of the angiogenesis the vascular density in the chorionic villi is significantly lower in the placental tissue from pregnancies with IUGR than from eutrophic pregnancies. It leads to worse placental blood flow and subsequently to the development of permanent hypoxia. My previously published results confirmed the increase of placental VEGF-A activity with angiogenic effect in intrauterine growth restriction that may compensate hypoxia resulting from vascular dysfunction.

20. The placental activity of endoglin showed no significant difference regarding the severity of intrauterine growth restriction. It can be assumed based on this finding that the severity of intrauterine growth restriction can be the result of other factors and not primarily of the antiangiogenic effect related to the placental endoglin.

21. Based on my findings the endoglin gene expression activity of placental samples from male and female fetuses did not show significant

difference. Gender has no considerable importance regarding the uteroplacental vascular insufficiency.

22. Endoglin gene overexpression could be observed in every case of intrauterine growth restriction independently from gestational age, however, it did not show significant correlation with the advancement of gestational age. It implies that the increase of the antiangiogenic effect as the underlying cause of IUGR may be present to the same extent in any gestational age.

23. Based on the birth weight, the ratio of newborns with severe (between 0 and 5 percentiles) intrauterine growth restriction was 30.7%, while of newborns with milder intrauterine growth restriction was 69.3%. It can be the result of the fact that in cases that did not or not sufficiently respond to the treatment and showed progression we decided to end the pregnancy in the majority of the cases due to the increasing risk of intrauterine complications.

24. The median value of gestational age in pregnancies with intrauterine growth restriction at delivery was 36±3.02 weeks, while in eutrophic pregnancies 38±1.76 weeks. Although there was no significant difference between the two values it can be observed that the pregnancies are ended earlier in the event of intrauterine retardation.

25. In the evaluated cases the intrauterine growth retardation proved to be significantly more common in girls than in boys; it can be assumed that it is only the result of the small sample size from epidemiological aspect and it cannot be traced back to pathophysiological correlations.

26. The median value of women's age delivering infants with IUGR showed no significant difference compared to the median value of pregnant women's age delivering eutrophic infants.

27. Pregnancies with intrauterine retardation were ended significantly more often with C-section. The most common indication for operation was imminent intrauterine asphyxia. My evaluations reinforced the assumption that the ability of the fetus to adapt to intrauterine insults, in particular to imminent hypoxic condition is worse in intrauterine growth restriction than in pregnancies with eutrophic growth.

28. The change of the Body Mass Index and the weight gain during pregnancy proved to be significantly smaller in intrauterine growth retardation than in eutrophic intrauterine development. It confirms that inadequate energy and nutrient input during pregnancy plays a considerable etiologic role in the development of intrauterine retardation.

LIST OF OWN LECTURES AND PUBLICATIONS

PUBLICATIONS RELATED TO THE THEME OF THE THESES

1. Rab A, Szentpéteri I, Kornya L, Börzsönyi B, Demendi C, Valent S, Zsom L, Hejja H, Joó JG
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Placental gene expression of Bax and Bcl-2 genes; apoptosis as a potential cause of intrauterine growth restriction
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1. Börzsönyi B, Demendi C, Nagy ZB, Szentpéteri I, Joó JG

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