pp. 82-85 (2014)

Predictive markers of intrauterine growth restriction

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Abstract

Intrauterine growth restriction is one of the most common and complex problem of the modern obstetrics. Common diseases of the adult as well as obesity, non-insulin dependent diabetes mellitus and cardiovascular disease appear to be related to the abnormal growing in the intrauterine life, in particular with intrauterine growth restriction. This paper aims to review some ultrasound markers (uterine artery Doppler velocimetry) and biomarkers (leptin, adiponectin, endothelin-1, lactate dehydrogenase, s-endoglin, growth factors secreted by placenta: soluble fms-like tyrosine kinase receptor-1, Pregnancy-associated Plasma Protein A, metastin (kisspeptin-54), cited in the literature of the recent years, that can predict uteroplacental insufficiency preceding the fetal intrauterine growth restriction. As an immediate effect, intrauterine growth restriction is associated with perinatal morbidity and increased mortality. Detecting the markers with the highest degree of predictivity, the early identification of this intrauterine fetal vulnerability allows an optimal preventive healthcare actions.

Keywords: *IUGR, placental insufficiency, Doppler, biomarkers*

Introduction

Fetuses with low weight for gestational age represent fetuses with the weight below the 10th percentile or below 2 DS. It can be found at a rate of 3-10% of all fetuses born alive. About 50-70% of them are perfectly healthy being constitutional small for the gestational age (SGA), do not show increased perinatal morbidity and mortality and requires minimal fetal monitoring.

The other category of fetuses with intrauterine growth restriction (IUGR) have small weight for the gestational age, where it can be suspected a placental insufficiency[(1)]. They have a lower growth potential, their perinatal morbidity and mortality is increased, requiring careful fetal monitoring and therapeutic interventions.

Most of the times, fetal intrauterine growth restriction has repercussions on the adult life, such as obesity, hypertension accompanied by chronic and non-insulin dependent diabetes.

There are two types of fetuses with intrauterine growth restriction: with symmetrical and with asymmetrical growth. Symmetrical growth restriction can be found in particular in fetal with genetic abnormalities (i.e. trisomy 18), infectious diseases (i.e. rubella, cytomegalovirus, toxoplasma, human Immunodeficiency virus, malaria[(2)], syphilis, listeriosis, tuberculosis, hepatitis A, hepatitis B[(3)]), malformations (20% of cases of IUGR), and aneuploidies in different syndromes (Cornelia de Lange)[(2)]. Asymmetric IUGR is usually associated with situations of nutritive and oxygen deprivation and also in placental insufficiency in pregnancy-induced hypertension.

The major cause of IUGR is represented by uteroplacental insufficiency caused by multifactorial etiology. Among the placental causes of uteroplacentar insufficiency it can be listed: chronic retroplacentar hematoma, placenta praevia, placental mosaicism, placental located trisomy 16, insertion of the umbilical cord marginal or velamentous, primary placental dysfunction and not the least, IUGR in the twin-to-twin transfusion syndrome from the twin monochorial pregnancy. Among the maternal causes of uteroplacental insufficiency it can be included: chronic lung disease, chronic renal disease, pre-existing diabetes in pregnancy, chronic hypertension, collagen disease, Crohn's disease, thrombophilia, antiphospholipid syndrome, factor V Leiden deficiency, prothrombin 20210A mutation. All this leads to a poor placentation, decreased placental blood flow and chronic hypoxemia[(2)].

The decrease of the placental blood flow leads to decreased transfer of to the fetus, and in a decline of the fetal liver reserves, which in the first phase can cause damage to the cellular dimensions and not to the their number. Consequently, it decreases the fetal liver size which translates into reduced waist circumference in disagreement with the head circumference that remains in the normal range for the gestational age[(4)].

Ultrasound Markers and Serum Biomarkers

This paper aims to review some ultrasound markers and serum biomarkers that have been cited in the literature in the recent years, which can predict uteroplacental insufficiency preceding fetal IUGR with or without preeclampsia.

Doppler ultrasound is a noninvasive method for determining maternal and fetal hemodynamics in pregnancy. The fetal IUGR caused by uteroplacental insufficiency, shares some common pathophysiological mechanisms of preeclampsia, and has a poor

Received: *March 21, 2014*
Revised: *June 02, 2014*
Accepted: *July 10, 2014*

trophoblastic invasion which translates into increased resistance in the uterine arteries.

Multiple studies have been published in the literature of recent years, which described the role of Doppler ultrasound in the prediction of uteroplacental insufficiency and the occurrence of IUGR with or without preeclampsia. In 2008, 74 studies were achieved about preeclampsia that included 79,547 pregnant women and 61 studies about iugr that included 41 131 pregnant women. From these studies it was concluded that the anomalies of arteries, seen by Doppler in the second trimester of pregnancy are the best predictive marker of preeclampsia and IUGR, namely measuring the pulsatility index with or without the presence of protodiastolic notch[5].

Among the prospective studies published later recall:

The team of researchers from the University of Barcelona in 2009, investigated by Doppler ultrasound, between 19-22 weeks a total of 6586 pregnant women. About 75 of them subsequently developed preeclampsia and 69 had fetuses with intrauterine growth restriction. They measured the pulsatility index in the uterine artery and obtained a good predictivity of its early forms of preeclampsia and intrauterine growth restriction.

Melchiorre and his collaborators analyzed the importance of first-trimester Doppler ultrasound of the uterine arteries in the prediction of intrauterine growth restriction and low weight fetuses for the gestational age. In their study that included 3202 pregnant women, it was measured indices of the uterine artery with transabdominal Doppler ultrasound between 12 and 14 weeks of gestation. Uterine artery resistivity index was higher in pregnancies with fetuses that were small for the gestational age, without no other associated pathology (0.602), higher in those who later developed intrauterine growth restriction (0.687), greater in infants with intrauterine growth restriction (0.776) and higher in small for gestational age fetuses with preeclamptic mothers (0.708)[6].

Regarding the biomarkers that can predict the IUGR among the Doppler ultrasound, it were made multiple studies in different universities and research centers around the world, in the desire to establish a series of indices that can appreciate the higher accuracy the increased risk of fetal IUGR. The value of the predictive biomarkers most studied in recent years have been: leptin, adiponectin, endothelin-1, lactate dehydrogenase, s-endoglin, growth factor secreted by the placenta: soluble fms-like tyrosine kinase receptor-1 (sFTL1), Pregnancy Associated Plasma Protein A and metastin (kisspeptin-54).

Leptin is an adipocyte protein, involved in homeostasis, with roles in reproduction and pregnancy. In pregnancy it is secreted by the placenta and has a role in determining fetal growth, placental angiogenesis, growth and immunomodulation, in breast adipose tissue mobilization. It can be detected in fetal plasma from 18 weeks of pregnancy[7].

Laivuori and collaborators have published a study in 2006 on the relationship between placental leptin gene expression, placental leptin protein concentration in maternal plasma, and leptin concentration in a group study of 79, of which 21 were preeclamptic and 20 had fetuses with IUGR, the rest of the women had normal pregnancy[8].

The studies of the reverse transcription polymerase chain reaction fragments of placenta, taken at birth and also maternal plasma samples, it were obtained the following results: placental leptin gene expression, placental protein of leptin concentration and leptin concentration in maternal plasma was higher in the group of 21 preeclamptic pregnant women, but not in the fetuses of pregnant women with IUGR[8]. Their conclusion is that it cannot establish a relationship between leptin levels and IUGR.

Maternal plasma leptin concentration was determined by RIA techniques and it were found significantly elevated plasma levels of mothers with fetuses with IUGR, both in the preeclamptic mothers group and in the group of normotensive mothers[9]. The conclusion was that leptin level is significantly increased in plasma of mothers with fetuses with intrauterine growth restriction, thus, it's increasing its heralds the onset of intrauterine growth restriction.

Kyriakakou and collaborators also supports the conclusions of the research team at the University of Kioto[10]. The same team in the same study analyzed the relationship between maternal serum adiponectin and IUGR. Adiponectin is a adipocytokine with crucial role in energetic metabolism, in insulin resistance, in inflammation and in the development of metabolic syndrome in adult life. It is a protein with an anti-inflammatory role, in contrast to leptin that is having pro-inflammatory properties. Researchers at the University of Athens included in their study a group of 40 women of whom 40 had fetuses with intrauterine growth restriction. If the maternal plasma leptin was significantly increased, the plasma concentration of adiponectin was low. They concluded that this pathology appears to be linked to a specific maternal profile, of increased concentration in serum leptin and lower concentration of adiponectin in mothers with fetuses with IUGR, possibly indicating a genetic predisposition for the development of insulin resistance[10].

Endothelin-1 is a potent vasoconstrictor product in the uteroplacentar vessels, in a high amount in the endothelial capillary cells and in the endothelial decidua and trophoblastic cells of the basal placental layer[11], related to the degree of hypoxia and to the deterioration of uteroplacental perfusion. In pregnancies with fetuses with IUGR it can be observed increased plasma levels of both maternal and fetal endotheline-1[12].

Margarit and collaborators studied the concentration of endothelin-1 in amniotic fluid in the second trimester at fetuses who will develop further restriction of growth, compared with fetuses that will develop normally. Amniotic fluid was collected from 125 preg-

nant women in the second trimester of pregnancy and endothelin-1 concentration was determined by RIA techniques. From the group of 125 pregnant women, 12 had fetuses that subsequently developed intrauterine growth restriction. Amniotic fluid taken from the pregnant women shown increased levels of endothelin-1 in comparison with the rest of the amniotic fluid samples taken from 113 pregnant women that had fetuses normally developed[13].

Borna and colleagues studied the amount of lactate dehydrogenase, ferritin and C reactive protein as predictive markers of IUGR in amniotic fluid collected in the 15 -20 weeks of gestation in a group of 110 pregnant women. Lactate dehydrogenase is a cytosolic enzyme which catalyzes the reversible oxidation of lactate to pyruvate in glycolysis and is a predictive marker of acute inflammation. In the present study it was found that a higher amount of LDH of 140 IU/L in the amniotic liquid has a predictive value of IUGR with a sensitivity of 87.5% and a specificity of 82.4%. It was unable to establish in the present study a relationship between the concentration of ferritin and C-reactive protein in the amniotic fluid and intrauterine growth restriction[14].

Wang and contributors published a study in which they analyzed the concentration of several angiogenic proteins such as s-endoglin (CD105 derived from placenta), sFlt1 (soluble fms-like tyrosine kinase receptor-1 that is a growth factor secreted by the placenta), leptin, adiponectin, and endothelin-1 in the amniotic fluid of 71 pregnant preeclamptic women of which 31 had fetuses with IUGR. Amniocentesis was performed between 16-19 weeks of gestation and it was taken 20 ml of amniotic fluid. It was found an increased concentration of sFlt1, s-endoglin and leptin in the amniotic fluid of pregnant women who subsequently developed preeclampsia. Increased levels of sFlt1, s-endoglin, leptin and endothelin-1 in amniotic fluid of preeclamptic pregnant women who subsequently had fetuses with intrauterine growth restriction. Leptin concentrations in amniotic fluid increases with about 2 months before the installation of the signs of IUGR. The authors further propose the use of leptin from amniotic fluid as a predictive marker in IUGR[15].

In 2009 Proctor and colleagues published an article on pregnancy-associated plasma protein A (PAPP-A), a predictive marker of IUGR and preeclampsia from normal genetically fetuses. In this study, 90 pregnant women were included. It was determined the concentration of PAPP-A between 11 and 13 weeks of gestation. They found low levels of placental protein both in pregnancies with fetuses affected of trisomy 21 and in pregnancies with fetuses who will further develop intrauterine growth restriction. The authors recommend determining the association of serum PAPP-A, maternal age and nuchal translucency ultrasound measurements[16].

Rizzo and his collaborators attempted to correlate the maternal serum PAPP-A and the umbilical venous flow between the weeks 11-14 of gestation with the IUGR. The authors appreciate the following: velocimetric decreased indices of the umbilical vein in the first trimester of pregnancy, associated with low concentration of PAPP-A in maternal serum, may be some accurate markers in predicting IUGR.

Smets and collaborators analyzed the concentration of metastin in maternal blood in the first trimester. The study had place between 2002-2004 on a sample of 870 pregnant women with gestational ages ranging from 8 to 14 weeks of which 242 were in a group at risk for preeclampsia, IUGR and Down syndrome. About 31 of pregnant women with fetuses in the study group who later developed IUGR had lower plasma levels of metastin compared to the rest of the pregnant women[17].

In 2009 Armstrong and his collaborators examined the metastin in maternal plasma in the second trimester of pregnancy. They also reached the conclusion that the metastin is decreased in pregnant women who will develop fetal IUGR[18].

Intrauterine growth restriction

IUGR is one of the most common and complex problems of modern obstetrics. Common diseases of the adult as non-insulin dependent diabetes mellitus and cardiovascular disease appear to be related to the abnormal development in the intrauterine life, in particular with IUGR.

Diagnosis and treatment of IUGR are ambiguous due to the lack of clear diagnostic criteria. Outside the fetal dimensions, the IUGR term should include the status of placental Doppler measurements determined by maternal, fetal biophysical serum, biomarkers and genetic markers[19].

Despite the progress of obstetrics, IUGR is associated with increased perinatal mortality and neonatal neurologic disease in 40%. It is responsible for 50% of the neonatal deaths in preterm births and for 20% of the term births[1].

Although IUGR is due to several factors such as chromosomal abnormalities, birth defects, infections, endogenous factors that affect the fetal intrauterine growth, the main cause is the poor transport of nutrients and oxygen from the mother to the fetus due to deficient trophoblastic invasion by remodeling inadequate maternal spiral arteries[17].

To decrease perinatal mortality and try to establish the optimal therapeutic conduct tasks in fetuses with IUGR, is important to establish the markers that can predict accurately the risk of fetal IUGR at preeclamptic mothers and also in the normotensive women.

Until present is not yet established an algorithm that has maximum predictivity for IUGR. It were tested different biomarkers which, with or without Doppler ultrasound have the highest predictive value in IUGR.

Leptin is detectable in fetal plasma from 18 weeks of pregnancy, its level is significantly increased in plasma of mothers with fetuses with IUGR, thus increasing its heralds the onset of IUGR. Leptin concentrations in

amniotic fluid increases with about 2 months before the installation of the signs of IUGR, for which it was proposed the use of leptin in amniotic fluid as a predictive marker in IUGR[15].

Plasma adiponectin concentration in maternal blood, conform to several studies, in contrast to leptin, has been shown to be decreased. From here, the conclusion was that it exist a specific maternal profile of increased serum leptin concentration and decreased level of the concentration of adiponectin from mothers with fetuses with IUGR, perhaps suggesting a genetic predisposition to developing insulin resistance.

Maternal and fetal plasma levels of endothelin-1 concentration in the amniotic fluid collected in the second trimester of pregnancy in women with fetuses that will develop IUGR is increased, which brings endothelin-1 biomarkers among the one very predictable in IUGR[12,13].

A higher value of lactate dehydrogenase of 140 IU/L in the amniotic fluid in a pregnancy in the second trimester has a predictive value of IUGR with a sensitivity of 87.5% and a specificity of 82.4%[14], supporting other studies.

Angiogenic proteins such as s-endoglin and sFLT1 increased in the amniotic fluid of pregnant women in the second trimester of pregnancy were also predictive in IUGR. Many studies comes in an attempt to establish the optimal formula for predicting IUGR associated with maternal serum PAPP-A and transvaginal or abdominal measurement of Doppler indices in uterine arteries or veins in the first trimester, claiming that one of these associations may be the most valuable in predicting IUGR and preeclampsia.

Studies from the last years have tried to establish the value of maternal plasma of metastin in predicting IUGR. It was found that low maternal metastin from serum in the second trimester of pregnancy may predict the risk of fetal IUGR.

Future Research

In conclusion, none of the markers listed above, disputed in many studies of recent years can not accurately establish the risk of fetal IUGR. The association between two or more ultrasound markers, serum or amniotic, can have a highly predictive value for IUGR. ■

References

1. Kurjak A, Fran A, Chervenak A. Donald School Textbook of Ultrasound in Obstetrics & Gynecology, 3rd Edition; 2011 Jaypee Brothers Medical Publishers Ltd; ISBN 978-93-5025-259-8, Cap 15.Ultrasound and Doppler Management of intrauterine growth restriction: Jose M Carrera, Francese Figueras, Eva Meler, 220-31.
2. Callen PW. Ultrasonography in Obstetrics and Gynecology; 5th Edition 2008; ISBN 978-1-4160-3264-9.
3. Cunningham S, Bloom L et al. William's Obstetrics 23 rd Edition 2010; The McGraw-Hill Companies, Inc; ISBN 978-0-07-149701-5 MHID 0-07-149701-3.
4. Haram K, Gjelland K. Foetal growth retardation. Tidsskr Nor Laegeforen 2007, 127(20), 2665-9.
5. Cnossen JS, Morris RK, Gerben ter Riet et al. Use of uterine artery Doppler ultrasonography to predict pre-eclampsia and intrauterine growth restriction: a systematic review and bivariable meta-analysis. CMAJ, 2008, 178(6), 5-8.
6. Melchiorre M, Leslie K., Prefumo F et al. First-trimester uterine artery Doppler indices in the prediction of small-for-gestational age pregnancy and intrauterine growth restriction; Ultrasound Obstet Gynecol 2009, 33, 524-9.
7. Hauguel-de Mouzon S, Lepercq J. Placental leptin and pregnancy pathologies;Gynecol Obstet Fertil 2001, 29(7-8), 534-7.
8. Laivuori H, Gallaher MJ, Collura L et al. - Relationships between maternal plasma leptin, placental leptin mRNA and protein in normal pregnancy, pre-eclampsia and intrauterine growth restriction without pre-eclampsia; Molecular Human Reproduction 2006, 12(9), 551-6.
9. Mise H, Yura S, Itoh H. The Relationship between maternal plasma leptin levels and fetal growth restriction. Endocrine Journal Japan 2007, 54(6), 945-51.
10. Kyriakakou M, Malamitsi-Puchner A, Militsi H. Leptin and adiponectin concentrations in intrauterine growth restricted and appropriate for gestational age fetuses, neonates, and their mothers. European Journal of Endocrinology 2008, 158, 343-8.
11. Erdem M, Erdem A, Erdem O et al. Immunohistochemical localization of endothelin-1 in human placenta from normal and growth-restricted pregnancies. Pediatr Dev Pathol 2003, 6(4), 307-13.
12. Al-Shahat Nezar M, Abd El-Baky AM, Al-Said Soliman O et al. Endothelin-1 and leptin as markers of intrauterine growth restriction. Indian Journal of Pediatrics, 76(5), 485-8.
13. Margarit L, Griffiths AN, Tsapanos V et al. Second trimester amniotic fluid endothelin-1 concentrations and subsequent development of intrauterine growth restriction. Eur J Obstet Gynecol Reprod Biol 2007, 134(2),192-5.
14. Borna S, Abdollahi A, Mirzaei F. Predictive value of mid-trimester amniotic fluid high-sensitive C-reactive protein, ferritin, and lactate dehydrogenase for fetal growth restriction Year. Indian J Pathol Microbiol 2009, 52(4), 498-500.
15. Chao-Nin Wang, Shuenn-Dyh Chang, Hsiu-Huei Peng et al. - Change in Amniotic Fluid Levels of Multiple Anti-Angiogenic Proteins before Development of Preeclampsia and Intrauterine Growth Restriction; J Clin Endocrinol Metab 2010, 95(3), 1431-41.
16. Proctor LK, Toal M, Keatingt S. et al. Placental size and the prediction of severe early-onset intrauterine growth restriction in women with low pregnancy-associated plasma protein-A. Ultrasound Obstet Gynecol 2009, 34, 274-82.
17. Nevo O, Many A, Xu J. Placental Expression of Soluble fms-Like Tyrosine Kinase 1 is Increased in Singletons and Twin Pregnancies with Intrauterine Growth Restriction. J Clin Endocrinol Metab 2008, 93(1):285-92.
18. Armstrong RA, Reynolds RM, Leask R et al. - Decreased serum levels of kisspeptin in early pregnancy are associated with intra-uterine growth restriction and pre-eclampsia. Prenat Diag 2009, 29(10), 982-5.
19. Zhang J, Merialdi M, Platt LD. Defining Normal and Abnormal Fetal Growth: Promises and Challenges. Am J Obstet Gynecol 2010, 202(6), 522-8.